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(54) Title: PHARMACEUTICAL COMPOSITIONS COMPRISING METAL COMPLEXES

(57) Abstract

A compound of the formula $[M_a(X_bL)_cY_dZ_e]^{n\pm}$ wherein: M is a metal ion or a mixture of metal ions; X is a cation or a mixture of cations; L is a ligand, or mixture of ligands each containing at least two different donor atoms selected from the elements of Group IV, Group V or Group VI of the Periodic Table; Y is a ligand or a mixture of the same or different ligands each containing at least one donor atom or more than one donor atom selected from the elements of Group IV, Group V or Group VI of the Periodic Table; and Z is a halide or pseudohalide ion or a mixture of halide ions and pseudohalide ions; and wherein: a=1–3; b=0–12; c=0–18; d=0–18; e=0–18; and n=0–10; provided that at least one of c, d and e is 1 or more; wherein c is 0: b is also 0; wherein a is 1: c, d and e are not greater than 9; and wherein a is 2: c, d and e are not greater than 12.

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PHARMACEUTICAL COMPOSITIONS COMPRISING METAL COMPLEXES

TECHNICAL FIELD

This invention relates to new pharmaceutical compositions and to pharmaceutical compositions having activity against diseases caused by, or related to, overproduction of localised high concentrations of reaction oxygen species, including nitric oxide, in the body.

BACKGROUND

Nitric oxide (NO) plays a varied and vital role in the body of a human or other mammals. For example, NO plays a vital role in the control of blood pressure: it acts as a neurotransmitter; it plays a role in inhibition of platelet aggregation (important in thrombosis or blockages of the blood vessels) and in cytostasis (important in fighting of tumours). Overproduction of NO however, has been implicated in a number of disease states, including vascular/pressor diseases such as septic shock, post-ischaemic cerebral damage, migraine and dialysis induced renal hypotension: immunopathologic diseases such as hepatic damage in inflammation and sepsis allograft rejection, graft versus host diseases, diabetes and wound healing: neurodegenerative diseases such as cerebral ischaemia, trauma, chronic epilepsy, Alzheimer's disease, Huntington's disease, and AIDS dementia complex; and side effects of treatment such as restenosis following angioplastic treatment and secondary hypotension following cytokine therapy.

Pharmacological modulation of nitric oxide or other reactive oxygen species in any of these disease states should prove extremely beneficial.

One above-mentioned disease relating to overproduction of NO is septic shock. This is precipitated by local septicaemnia or endotoxaemia, (high local levels of bacterial endotoxins). The result is activation of macrophages, lymphocytes, endothelial cells and other cell types capable of producing NO further mediated by cytokine production by these cells. The activated macrophages produce excess NO which causes vasodilation of the blood vessels, and results in local vascular damage and vascular collapse. This destruction of vascular integrity may be so great that it leads to the collapse of haemodynanic homeostasis, the end result being death.

Current ideas for pharmacological modulation of nitric oxide in such diseases are based on dealing with the mediators of septic shock such as cytokines, endotoxins and platelet activating factor (PAF). The approaches include use of antibodies to cytokines such as tumour necrosis factor (TNF) receptor antagonists such as interleukin I (IL-1) antibodies to lipopolysaccharide (the endotoxins produced by Gram negative bacteria) and PAF antagonists. All such approaches while challenging a factor mediating septic shock do not attempt to deal with the aetiology or cause of the disease. Recent advances in understanding of NO have lead to the proposal that inhibitors of the NO synthase enzyme such as N^G-monomethy-L-arginine (L-NMMA) may be useful in the treatment of septic shock and other NO overproduction related to diseases since they inhibit NO production. While these inhibitors have shown some utility in animal models and preliminary clinical studies they have the disadvantage of undesirably inhibiting total NO synthesis in the body.

An aim of the present invention is to provide new compositions which are able to modulate levels of NO and other reactive oxygen species in the body. Examples of other reactive species include superoxide, hydroxyl radical, peroxide, peroxynitrite, and other oxides of nitrogen including protein adducts. The compositions of metal complexes described herein are able to carry out the important role of reducing levels of these harmful species by scavenging.

SUMMARY OF THE INVENTION

Some metal complexes are known in pharmaceutical compositions for the treatment of diseases of the body of a human or other mammal. For example certain complexes of platinum and ruthenium have been used or indicated in the treatment of cancer. Metal complexes have not however been previously indicated in the treatment of disease relating to the overproduction of reactive oxygen species (including the overproduction of NO).

This invention provides for the use of a neutral anionic or cationic metal complex having at least one site for coordination with NO of Formula I

$$[M_a(XbL)_cY_dZ_e]^{n\pm} \quad \text{Formula I}$$

in the manufacture of a medicament for the attenuation of NO levels and other reactive oxygen species when implicated in disease.

where:

M is a metal ion or a mixture of metal ions:

X is a cation or a mixture of cations:

L is a ligand, or mixture of ligands each containing at least two different donor atoms selected from the elements of Group IV, Group V or Group VI of the Periodic Table;

Y is a ligand or a mixture of the same or different ligands each containing at least one donor atom or more than one donor atom which donor atom is selected from the elements of Group IV, Group V or Group VI of the Periodic Table:

And

Z is a halide or pseudohalide ion or a mixture of halide ions and pseudohalide ions:

a=1-3; b=0-12; c=0-18; d=0-18; e=0-18; and n=0-10; provided that at least one of c, d and e is 1 or more.

And where c is 0: b is also 0;

And where a is 1: c, d and e are not greater than 9;

And where a is 2: c, d and e are not greater than 12.

By "complex" in this specification is meant a neutral complex or anionic or cationic species.

The term "Group" which is used herein is to be understood as a vertical column of the periodic table in which elements of each Group have similar physical and chemical properties. The definition of the Periodic Table is that credited to Mendeleev; Chamber Dictionary of Science and Technology, 1974 Published by W & R Chambers Ltd. The nomenclature of the compounds as disclosed herein are based upon common usage. The names of the compounds according to nomenclature of the American Chemical Abstracts Service (American Chemical Society) are also provided in Table 5.

This invention may also be stated as providing a method of attenuation of reactive oxygen species when implicated in diseases of the human body or the bodies of other mammals. Thus the invention comprises administering a pharmaceutical composition containing a neutral, anionic or cationic metal complex of Formula I.

This invention may also provide for the use of a neutral anionic or cationic metal complex of formula I in the manufacture of a medicament for the treatment of

diseases in which reactive oxygen species are overproduced.

This invention may also be stated as providing a method of attenuation of nitric oxide when implicated in diseases of the human body or bodies of other mammals. Thus the invention comprises administering a pharmaceutical composition containing a neutral, anionic or cationic metal complex of Formula I.

This invention may also be stated as providing a method of treatment of diseases of a body of a human or other mammals resultant of overproduction of NO in the body comprising administering a pharmaceutical composition containing a neutral anionic or cationic metal complex of formula I.

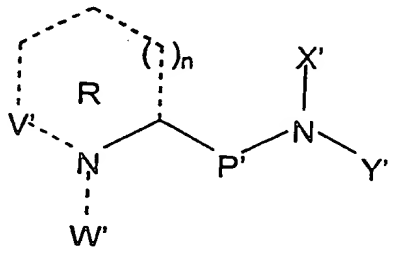
Where the formula I represents an anionic species a cation will also be present. Where formula I represent a cationic species an anion will also be present. The metal complexes may be hydrated.

Preferably M is a first, second or third row transition metal ion. For example M may be an Rh, Ru, Os, Mn, Co, Cr or Re ion, and is preferably an Rh, Ru or Os ion.

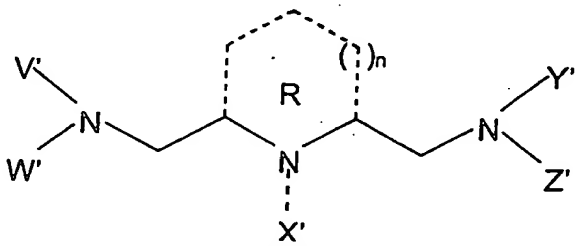
Suitably M is in an oxidation state III. We have found surprisingly that when the metal ion for example ruthenium is in oxidation state III, the rate at which it binds with NO is significantly faster than when it is in oxidation state II.

X may be any cation, such as mono-, di- or tri-valent cation. Suitable cations may be H^+, K^+, Na^+, NH_4^+ or Ca^{2+}. Conveniently X may be H^+, K^+, or Na^+.

Preferably L is a polyaminocarboxylate ligand described herein by the general formulae A and B:



Formula A



Formula B

Where:

V', W', X', Y' and Z' are independently selected selected from H, phenyl,

heteroaryl, C_{1-6}alkyl, C_{1-6}alkylhydroxy, C_{1-6}alkylthiol, C_{1-6}alkylaryl, C_{1-6}alkylheteroaryl, C_{1-6}alkylheterocyclyl and derivatives thereof. Preferred alkylheterocyclic groups are pyridinylmethylene, pyrazinylmethylene, pyrimidinylmethylene. The aromatic and heteroaromatic groups may be suitably substituted in single or multiple positions with halide, C_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}alkoxyaryl or benzyloxy, hydroxy, C_{1-6}hydroxyalkyl, thiol, carboxylic acid, carboxyalkylC_{1-6}, carboxamide, carboxamidoalkylC_{1-6}, anilide.

P' = CH_2, $(CH_2)_2$, $CHOHCH_2$, $CH(OC_{1-6}alkyl)CH_2$

V', W', X', Y' and Z' may also be methylenecarboxylic acid, methylenecarboxyC_{1-6}alkyl, methylenecarboxamideC_{1-6}alkyl or heterocyclyl, methylenecarboxanilide, methylenecarboxamido derivatives of an aminoacid or peptide, methylenehydroxamic acid, methylene phosphonic acid, C_{1-6}alkylthiol.

In the above formulae, the ligands may be optionally fused with a heterocyclic ring R (n= 0 or 1). Prefered heterocyclic groups are pyridine, pyrimidine, pyrazine, imidazole, thiazole, oxazole.

More preferably L is a ligand such as ethylenediamine-N,N'-diacetic acid (edda), ethylenediaminetetraacetic acid (edta), nitrilotriacetic acid (nta), dipicolinic acid (dipic), picolinic acid (pic), diethylenetri-aminepentaacetic acid (dtpa), thiobis(ethylenenitrilo)tetraacetic acid (tedta), dithioethanebis(ethylenenitrilo)tetraacetic acid (dtedta), and N-(2-hydroxethyl) ethylenediamine-triacetic acid (hedtra).

Preferably Y is a ligand containing nitrogen, oxygen, sulphur, carbon or phosphorus donor groups. Suitable nitrogen donor groups may be for example ammine, amine, nitrile and nitride or derivations thereof. Suitable oxygen donor groups may be for example carboxylic acid, ester or derivations thereof, water, oxide, sulphoxide, hydroxide, acetate, lactate, propionate, oxalate and maltolate. Suitable sulphur donor groups may be for example sulphoxide, dialkysulphide, dithiocarbamate or dithiophosphate. Suitable carbon donor groups may be for example carbon monoxide or isocyanide. Suitable phosphorus donor groups may be for example trialkylphosphine.

Z may be any halide and is preferably chloride, bromide or iodide. Most conveniently, Z is chloride.

Examples of metal complexes for use according to the present invention include optionally hydrated ruthenium complexes of Formula II

$$[Ru(H_{0-6}\,L^{II})_{1-3}Y_{0-2}Cl_{0-4}\,]^{(0-4)\pm} \qquad \text{Formula II}$$

where L^{II} is a polyaminocarboxylate ligand as already described herein by the general formulae A and B, more preferably a polydentate aminocarboxylate ligand such as, for example edta, nta, dipic, pic, edda, tropolone, dtpa, hedtra, tedta or dtedta or diamide of edta or dtpa (or an amide or ester derivative thereof) or a mixture of any of these and Y is as defined above and may for example be selected from: acetylacetone (acac) a β-diketonate; water; dimethylsulphoxide (dmso); carboxylate; bidentate carboxylate; catechol; kojiic acid; maltol; hydroxide; tropolone; malonic acid; oxalic acid; 2.3-dihydroxynaphthalene; squaric acid; acetate; a sulphate and a glycolate.

The skilled artisan will be able to substitute other known ligands at Y and which will fall within the scope of the inventions.

Preparative methods of tedta, dtedta and diamide of edta and dtpa are described in the following references respectively:

P Tse & JE Powell, Inorg Chem, (1985), 24, 2727

G Schwartzenbach, H Senner, G Anderegg, Helv Chim Acta 1957, 40, 1886

MS Konings, WC Dow, DB Love, KN Raymond, SC Quay and SM Rocklage, Inorg Chem (1990), 29, 1488-1491

PN Turowski, SJ Rodgers, RC Scarrow and KN Raymond, Inorg Chem (1988), 27, 474-481.

Where the complex of Formula II is an anion, a cation will be required. For example the complexes of Formula II are present in

$K[Ru(Hedta)Cl]2H_2O$

$[Ru(H_2edta)(acac)]$

$K[Ru(hedtra)Cl]H_2O$

$K[Ru(dipic)_2]H_2O$

$(H_2pic)[RuCl_2(pic)_2](Hpic)H_2O$

$K[Ru(H_2edta)Cl_2]H_2O$

$K[Ru(Hnta)_2]½H_2O$

$K[Ru(H_2dtpa)Cl]H_2O$

[Ru(Hhedtra)acac]H_2O

[Ru(Hhedtra)trop]

[Ru(H_3dtpa)Cl]

Complexes of formula II have not to the best of our knowledge been previously indicated in any pharmaceutical composition. Therefore the present invention also provides a pharmaceutical composition containing an optionally hydrated ruthenium complex of Formula II.

Further examples of metal complexes for use according to the present invention include optionally hydrated complexes of Formula III

$[M_{1-3}Y_{1-18}Cl_{0-18}]^{(0-6)\pm}$ Formula III

where Y is a sulphur donor ligand. For example, such complex is present in

[Ru(mtc)$_3$] (mtc = 4-morpolinecarbodithoic acid)

$Ru(S_2CNCH_2CH_2NMeCH_2CH_2)_3$½$H_2O$

Complexes of Formula III in which Y is a sulphur donor ligand have not to the best of our knowledge been previously indicated in any pharmaceutical composition. Therefore, the present invention also provides a pharmaceutical composition containing an optionally hydrated complex of Formula III when Y is a sulphur donor ligand.

Yet further examples of metal complexes for use according to the present invention include optionally hydrated complexes of ruthenium of Formula III

$[M^{III}{}_{1-3}Y^{III}{}_{1-18}Cl_{0-18}]^{(0-6)\pm}$ Formula III

where M^{III} is ruthenium and Y^{III} is an oxygen-donor ligand such as acetate, lactate, water, oxide, propionate (COEt), oxalate (ox), or maltolate (maltol) or a combination of these. For example complexes of Formula III are present in

$[Ru_3O(OAc)_6](OAc)$

$[Ru_3O(lac)_6](lac)$

$[Ru_2(OAc)_4]NO_3$

$[Ru_2(OCOEt)_4]NO_3$

$K_3[Ru(ox)_3]$

$[Ru_2(OAc)_4]Cl$

[Ru(maltol)$_3$]

Some complexes of Formula III have not to the best of our knowledge been previously indicated in any pharmaceutical composition. Therefore the present invention also provides a pharmaceutical composition containing an optionally hydrated complex of ruthenium of Formula III wherein M^{III} is ruthenium and Y^{III} is an oxygen-donor ligand selected from the group acetate, lactate, oxide, propionate and maltolate.

Further examples of metal complexes for use according to the present invention include optionally hydrated complexes of ruthenium of Formula IV

$[RuY^{IV}_{1-9}Cl_{1-9}]^{(0-4)\pm}$ Formula IV

where Y^{IV} is a nitrogen-donor ligand such as: ammine; ethylenediamine (en); pyridine (py); 1,10-phenanthroline (phen): 2,2-bipyridine (bipy) or 1,4,8,11-tetraazacyclotetradecane (cyclam); 1,4,7-triazacyclononane; 1,4,7-triazacyclononane tris acetic acid; 2,3,7,8,12,13,17,18-octaethylporphyrin (oep); or a combination of these. For example complexes of Formula IV are present in

$[Ru(H_3N)_5Cl]Cl_2$

$[Ru(en)_3]I_3$

trans-$[RuCl_2(py)_4]$

$K[Ru(phen)Cl_4]$

$[Ru(cyclam)Cl_2]Cl$

$K[Ru(bipy)Cl_4]$

$[Ru(NH_3)_6]Cl_3$

$[Ru(NH_3)_4Cl_2]Cl$

Ru(oep)Ph

Some complexes of Formula IV have not to the best of our knowledge been previously indicated in any pharmaceutical composition. Therefore the present invention also provides a pharmaceutical composition containing an optionally hydrated complex of ruthenium of Formula IV wherein Y^{IV} is a nitrogen-donor ligand selected from the group en, py, phen, bipy, cyclam and oep. Derivations of these ligands can be prepared by a skilled artisan and which will fall within the scope of the inventions.

Still further examples of metal complexes for use according to the present invention invlude optionally hydrated complexes of ruthenium or osmium of general Formula V

$$[M_{1-3}Y^{V}_{1-18}Cl_{0-18}]^{(0-6)\pm} \qquad \text{Formula V}$$

where Y^V is a combination of donor ligands such as are described hereinabove, for example ammine, dmso, oxalate, bipy, acac and methyl cyanide. Complexes of Formula V are present in for example

$[Ru(NH_3)(dmso)_2Cl_3]$

cis-$[Ru(dmso)_4Cl_2]$

cis-$[Ru(NH_3)(dmso)_3Cl_2]$

$[Ru(dmso)_3Cl_3]$

$[Os(ox)(bipy)_2]H_2O$

$[Ru(acac)_2(MeCN)_2]CF_3SO_3$

The complex ions of the latter two compounds above have not to the best of our knowledge been previously indicated in any pharmaceutical composition. Therefore the present invention also provides a pharmaceutical composition containing an optionally hydrated complex of formula $[Os(ox)(bipy)_2]$; and further a pharmaceutical composition containing an optionally hydrated complex of formula $[Ru(acac)_2(MeCN)_2]^+$.

In use the complexes of the present invention may be included as an active component in a pharmaceutical composition containing an optionally hydrated complex of any of Formulae I-V, in admixture with a pharmaceutically acceptable carrier or diluent. Said pharmaceutical composition may be formulated according to well known principles, and may be in the form of a solution or suspension for parenteral administration in single or repeat doses or be in capsule, tablet, dragee, or other solid composition or as a solution or suspension for oral administration, or formulated into pessaries or suppositories, or sustained release forms of any of the above. The solution or suspension may be administered by a single or repeat bolus injection or continuous infusion, or any other desired schedule. Suitable diluents, carriers, excipients and other components are known. Said pharmaceutical composition may contain dosages determined in accordance with conventional pharmacological methods, suitable to provide active complexes in the dosage range in

humans of 1mg to 10g per day and dosages in other mammals as determined by routine clinical veterinary practice. Actual required dosage is largely dependent on where in the body there is the excess concentration of NO or other reactive oxygen species and for how long overproduction continues or attenuation of the levels of NO or reactive oxygen species, where such reactive oxygen species is implicated in disease, is required.

BRIEF DESCRIPTION OF THE DRAWINGS

The foregoing aspects and many of the attendant advantages of this invention will become more readily appreciated as the same becomes better understood by reference to the following detailed description, when taken in conjunction with the accompanying drawings, wherein:

FIGURE 1 illustrates pressure changes induced by the compounds of the present invention, which reflect a reduction in available nitric oxide compared with control levels.

FIGURE 2 shows the available nitric oxide concentration (micromoles/liter) following reaction of nitric oxide with compounds of the present invention as compared with control levels.

FIGURE 3 demonstrates the inhibition of tumour growth by AMD6245 and AMD6221.

FIGURE 4A-4G provides chemical structural formulas for the AMD-numbered compounds disclosed.

FIGURE 5A-5C provides chemical structural formulas for the AMD-numbered compounds disclosed.

DETAILED DESCRIPTION OF THE INVENTION

Introduction and General Description of the Invention

This invention is directed to metal complexes which are useful in binding nitric oxide with sufficiently high affinity as to make such complexes useful as pharmaceutical compositions for the treatment of diseases in mammals, preferably in the human body.

Some metal complexes are known in pharmaceutical compositions for the treatment of diseases in mammals, preferably in diseases of the human body. For example certain complexes of platinum and ruthenium have been used or indicated in

the treatment of cancer. Metal complexes have not however been previously indicated in the treatment of disease relating to the overproduction of reactive oxygen species (including the overproduction of NO). This invention provides for the use of a neutral anionic or cationic metal complex having at least one site for coordination with NO of Formula I

$[M_a(XbL)_cY_dZ_e]^{nt\pm}$ Formula I

in the manufacture of a medicament for the attenuation of NO levels and other reactive oxygen species when implicated in disease.

where:

M is a metal ion or a mixture of metal ions:

X is a cation or a mixture of cations:

L is a ligand, or mixture of ligands each containing at least two different donor atoms selected from the elements of Group IV, Group V or Group VI of the Periodic Table;

Y is a ligand or a mixture of the same or different ligands each containing at least one donor atom or more than one donor atom which donor atom is selected from the elements of Group IV, Group V or Group VI of the Periodic Table:

And

Z is a halide or pseudohalide ion or a mixture of halide ions and pseudohalide ions:

a=1-3; b=0-12; c=0-18; d=0-18; e=0-18; and n=0-10; provided that at least one of c, d and e is 1 or more.

And where c is 0: b is also 0;

And where a is 1: c, d and e are not greater than 9;

And where a is 2: c, d and e are not greater than 12.

By "complex" in this specification is meant a neutral complex or anionic or cationic species.

The term "Group" which is used herein is to be understood as a vertical column of the periodic table in which elements of each Group have similar physical and chemical properties. The definition of the Periodic Table is that credited to Mendeleev; Chamber Dictionary of Science and Technology, 1974 Published by W & R Chambers Ltd. The nomenclature of the compounds as disclosed herein are based

upon common usage. The names of the compounds according to nomenclature of the American Chemical Abstracts Service (American Chemical Society) are also provided in Table 5.

This invention may also be stated as providing a method of attenuation of reactive oxygen species when implicated in diseases in mammals, preferably in diseases of the human body. Thus the invention comprises administering a pharmaceutical composition containing a neutral, anionic or cationic metal complex of Formula I.

This invention may also provide for the use of a neutral anionic or cationic metal complex of formula I in the manufacture of a medicament for the treatment of diseases in mammals, preferably in diseases of the human body in which reactive oxygen species are overproduced.

This invention may also be stated as providing a method of attenuation of nitric oxide when implicated in diseases in mammals, preferably in diseases of the human body. Thus the invention comprises administering a pharmaceutical composition containing a neutral, anionic or cationic metal complex of Formula I.

This invention may also be stated as providing a method of treatment of diseases of the human body resultant of overproduction of NO in the human body comprising administering a pharmaceutical composition containing a neutral anionic or cationic metal complex of formula I.

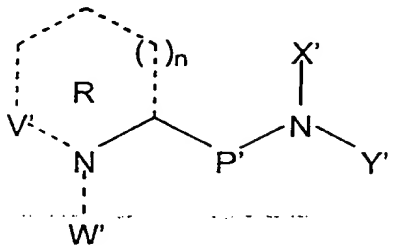
Where the formula I represents an anionic species a cation will also be present. Where formula I represent a cationic species an anion will also be present. The metal complexes may be hydrated.

Preferably M is a first, second or third row transition metal ion. For example M may be an Rh, Ru, Os, Mn, Co, Cr or Re ion, and is preferably an Rh, Ru or Os ion.

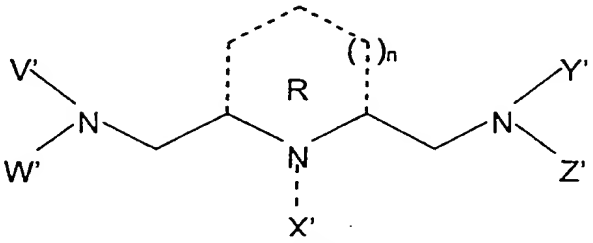
Suitably M is in an oxidation state III. We have found surprisingly that when the metal ion for example ruthenium is in oxidation state III, the rate at which it binds with NO is significantly faster than when it is in oxidation state II.

X may be any cation, such as mono-, di- or tri-valent cation. Suitable cations may be H^+, K^+, Na^+, NH_4^+ or Ca^{2+}. Conveniently X may be H^+, K^+, or Na^+.

Preferably L is a polyaminocarboxylate ligand described herein by the general formulae A and B:



Formula A



Formula B

Where:

V', W', X', Y' and Z' are independently selected from H, phenyl, heteroaryl, C_{1-6}alkyl, C_{1-6}alkylhydroxy, C_{1-6}alkylthiol, C_{1-6}alkylaryl, C_{1-6}alkylheteroaryl, C_{1-6}alkylheterocyclyl and derivatives thereof. Preferred alkylheterocyclic groups are pyridinylmethylene, pyrazinylmethylene, pyrimidinylmethylene. The aromatic and heteroaromatic groups may be suitably substituted in single or multiple positions with halide, C_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}alkoxyaryl or benzyloxy, hydroxy, C_{1-6}hydroxyalkyl, thiol, carboxylic acid, carboxyalkylC_{1-6}, carboxamide, carboxamidoalkylC_{1-6}, anilide.

P' = CH_2, $(CH_2)_2$, $CHOHCH_2$, $CH(OC_{1-6}alkyl)CH_2$

V', W', X', Y' and Z' may also be methylenecarboxylic acid, methylenecarboxyC_{1-6}alkyl, methylenecarboxamideC_{1-6}alkyl or heterocyclyl, methylenecarboxanilide, methylenecarboxamido derivatives of an aminoacid or peptide, methylenehydroxamic acid, methylene phosphonic acid, C_{1-6}alkylthiol.

In the above formulae, the ligands may be optionally fused with a heterocyclic ring R (n= 0 or 1). Prefered heterocyclic groups are pyridine, pyrimidine, pyrazine, imidazole, thiazole, oxazole.

More preferably L is a ligand such as ethylenediamine-N,N'-diacetic acid (edda), ethylenediaminetetraacetic acid (edta), nitrilotriacetic acid (nta), dipicolinic acid (dipic), picolinic acid (pic), diethylenetri-aminepentaacetic acid (dtpa), thiobis(ethylenenitrilo)tetraacetic acid (tedta), dithioethanebis(ethylenenitrilo)tetraacetic acid (dtedta), and N-(2-hydroxethyl) ethylenediamine-triacetic acid (hedtra).

Preferably Y is a ligand containing nitrogen, oxygen, sulphur, carbon or phosphorus donor groups. Suitable nitrogen donor groups may be for example ammine, amine, nitrile and nitride or derivations thereof. Suitable oxygen donor groups may be for example carboxylic acid, ester or derivations thereof, water, oxide, sulphoxide, hydroxide, acetate, lactate, propionate, oxalate and maltolate. Suitable sulphur donor groups may be for example sulphoxide, dialkysulphide, dithiocarbamate or dithiophosphate. Suitable carbon donor groups may be for example carbon monoxide or isocyanide. Suitable phosphorus donor groups may be for example trialkylphosphine.

Z may be any halide and is preferably chloride, bromide or iodide. Most conveniently, Z is chloride.

Examples of metal complexes for use according to the present invention include optionally hydrated ruthenium complexes of Formula II

$$[Ru(H_{0-6}\,L^{II})_{1-3}Y_{0-2}Cl_{0-4}]^{(0-4)\pm} \qquad \text{Formula II}$$

where L^{II} is a

Preferably L is a polyaminocarboxylate ligand as already described herein by the general formulae A and B. More preferably, L is a polydentate aminocarboxylate ligand, for example edta, nta, dipic, pic, edda, tropolone, dtpa, hedtra, tedta or dtedta or diamide of edta or dtpa (or an amide or ester derivative thereof) or a mixture of any of these and Y is as defined above and may for example be selected from: acetylacetone (acac) a β-diketonate; water; dimethylsulphoxide (dmso); carboxylate; bidentate carboxylate; catechol; kojiic acid; maltol; hydroxide; tropolone; malonic acid; oxalic acid; 2.3-dihydroxynaphthalene; squaric acid; acetate; a sulphate and a glycolate. The skilled artisan will be able to substitute other known ligands at Y and which will fall within the scope of the inventions.

Preparative methods of tedta, dtedta and diamide of edta and dtpa are described in the following references respectively:

P Tse & JE Powell, Inorg Chem, (1985), 24, 2727

G Schwartzenbach, H Senner, G Anderegg, Helv Chim Acta 1957, 40, 1886

MS Konings, WC Dow, DB Love, KN Raymond, SC Quay and SM Rocklage, Inorg Chem (1990), 29, 1488-1491

PN Turowski, SJ Rodgers, RC Scarrow and KN Raymond, Inorg Chem (1988), 27, 474-481.

Where the complex of Formula II is an anion, a cation will be required. For example the complexes of Formula II are present in

$K[Ru(Hedta)Cl]2H_2O$

$[Ru(H_2edta)(acac)]$

$K[Ru(hedtra)Cl]H_2O$

$K[Ru(dipic)_2]H_2O$

$(H_2pic)[RuCl_2(pic)_2](Hpic)H_2O$

$K[Ru(H_2edta)Cl_2]H_2O$

$K[Ru(Hnta)_2]½H_2O$

$K[Ru(H_2dtpa)Cl]H_2O$

$[Ru(Hhedtra)acac]H_2O$

[Ru(Hhedtra)trop]

$[Ru(H_3dtpa)Cl]$

Complexes of formula II have not to the best of our knowledge been previously indicated in any pharmaceutical composition. Therefore the present invention also provides a pharmaceutical composition containing an optionally hydrated ruthenium complex of Formula II.

Further examples of metal complexes for use according to the present invention include optionally hydrated complexes of Formula III

$[M_{1-3}Y_{1-18}Cl_{0-18}]^{(0-6)\pm}$ Formula III

where Y is a sulphur donor ligand. For example, such complex is present in

$[Ru(mtc)_3]$ (mtc = 4-morpolinecarbodithoic acid)

$Ru(S_2CNCH_2CH_2NMeCH_2CH_2)_3½H_2O$

Complexes of Formula III in which Y is a sulphur donor ligand have not to the best of our knowledge been previously indicated in any pharmaceutical composition. Therefore, the present invention also provides a pharmaceutical composition containing an optionally hydrated complex of Formula III when Y is a sulphur donor ligand.

Yet further examples of metal complexes for use according to the present invention include optionally hydrated complexes of ruthenium of Formula III

$[M^{III}_{1-3}Y^{III}_{1-18}Cl_{0-18}]^{(0-6)\pm}$ Formula III

where M^{III} is ruthenium and Y^{III} is an oxygen-donor ligand such as acetate, lactate, water, oxide, propionate (COEt), oxalate (ox), or maltolate (maltol) or a combination of these. For example complexes of Formula III are present in

$[Ru_3O(OAc)_6](OAc)$

$[Ru_3O(lac)_6](lac)$

$[Ru_2(OAc)_4]NO_3$

$[Ru_2(OCOEt)_4]NO_3$

$K_3[Ru(ox)_3]$

$[Ru_2(OAc)_4]Cl$

$[Ru(maltol)_3]$

Some complexes of Formula III have not to the best of our knowledge been previously indicated in any pharmaceutical composition. Therefore the present invention also provides a pharmaceutical composition containing an optionally hydrated complex of ruthenium of Formula III wherein M^{III} is ruthenium and Y^{III} is an oxygen-donor ligand selected from the group acetate, lactate, oxide, propionate and maltolate.

Further examples of metal complexes for use according to the present invention include optionally hydrated complexes of ruthenium of Formula IV

$[RuY^{IV}_{1-9}Cl_{1-9}]^{(0-4)\pm}$ Formula IV

where Y^{IV} is a nitrogen-donor ligand such as: ammine; ethylenediamine (en); pyridine (py); 1,10-phenanthroline (phen): 2,2-bipyridine (bipy) or 1,4,8,11-tetraazacyclotetradecane (cyclam); 2,3,7,8,12,13,17,18-octaethylporphyrin (oep); or a combination of these. For example complexes of Formula IV are present in

$[Ru(HN_3)_5Cl]Cl_2$

$[Ru(en)_3]I_3$

trans-$[RuCl_2(py)_4]$

$K[Ru(phen)Cl_4]$

$[Ru(cyclam)Cl_2]Cl$

$K[Ru(bipy)Cl_4]$

$[Ru(NH_3)_6]Cl_3$

$[Ru(NH_3)_4Cl_2]Cl$

Ru(oep)Ph

Some complexes of Formula IV have not to the best of our knowledge been previously indicated in any pharmaceutical composition. Therefore the present invention also provides a pharmaceutical composition containing an optionally hydrated complex of ruthenium of Formula IV wherein Y^{IV} is a nitrogen-donor ligand selected from the group en, py, phen, bipy, cyclam and oep. Derivations of these ligands can be prepared by a skilled artisan and which will fall within the scope of the inventions.

Still further examples of metal complexes for use according to the present invention include optionally hydrated complexes of ruthenium or osmium of general Formula V

$$[M_{1-3}Y^{V}_{1-18}Cl_{0-18}]^{(0-6)\pm} \qquad \text{Formula V}$$

where Y^{V} is a combination of donor ligands such as are described hereinabove, for example ammine, dmso, oxalate, bipy, acac and methyl cyanide. Complexes of Formula V are present in for example

$[Ru(NH_3)(dmso)_2Cl_3]$

cis-$[Ru(dmso)_4Cl_2]$

cis-$[Ru(NH_3)(dmso)_3Cl_2]$

$[Ru(dmso)_3Cl_3]$

$[Os(ox)(bipy)_2]H_2O$

$[Ru(acac)_2(MeCN)_2]CF_3SO_3$

The complex ions of the latter two compounds above have not to the best of our knowledge been previously indicated in any pharmaceutical composition. Therefore the present invention also provides a pharmaceutical composition containing an optionally hydrated complex of formula $[Os(ox)(bipy)_2]$; and further a pharmaceutical composition containing an optionally hydrated complex of formula $[Ru(acac)_2(MeCN)_2]^{+}$.

In use the complexes of the present invention may be included as an active component in a pharmaceutical composition containing an optionally hydrated complex of any of Formulae I-V, in admixture with a pharmaceutically acceptable carrier or diluent. Said pharmaceutical composition may be formulated according to well known principles, and may be in the form of a solution or suspension for

parenteral administration in single or repeat doses or be in capsule, tablet, dragee, or other solid composition or as a solution or suspension for oral administration, or formulated into pessaries or suppositories, or sustained release forms of any of the above. The solution or suspension may be administered by a single or repeat bolus injection or continuous infusion, or any other desired schedule. Suitable diluents, carriers, excipients and other components are known. Said pharmaceutical composition may contain dosages determined in accordance with conventional pharmacological methods, suitable to provide active complexes in the dosage range in humans of 1mg to 10g per day. Actual required dosage is largely dependent on where in the body there is the excess concentration of NO or other reactive oxygen species and for how long overproduction continues or attenuation of the levels of NO or reactive oxygen species, where such reactive oxygen species is implicated in disease, is required. It will be understood that the present invention may be used in combination with any other pharmaceutical composition useful for this purpose.

Citation of the above documents is not intended as an admission that any of the foregoing is pertinent prior art. All statements as to the date or representation as to the contents of these documents is based on the information available to the applicants and does not constitute any admission as to the correctness of the dates or contents of these documents. Further, all documents referred to throughout this application are incorporated in their entirety by reference herein. Terms as used herein are based upon their art recognized meaning unless otherwise indicated and should be clearly understood by the ordinary skilled artisan.

EXAMPLES

Having now generally described the invention, the same will be more readily understood through reference to the following examples which are provided by way of illustration, and are not intended to be limiting of the present invention, unless specified.

A number of commercially available compounds, and compounds prepared by routes known in the literature, containing the complexes of the present invention were tested *in vitro*, *in vitro* cell culture, and *ex vivo* in order to determine ability to coordinate with NO. The complexes tested were as follows:

Table 1

Example	Compound	Literature Reference for Preparation
1	$K[Ru(hedta)Cl]2H_2O$	AA Diamantis & JV Dubrawski, Inorg. Chem. (1981) 20:1142-50
2	$[Ru(H_2edta)(acac)]$	AA Diamantis & JV Dubrawski, Inorg. Chem. (1983) 22:1934-36
3	$K[Ru(hedtra)Cl]H_2O$	HC Bajaj & R van Eldik, Inorg. Chem. (1982) 28:1980-3
4	$K[Ru(dipic)_2]H_2O$	NH Williams & JK Yandell, Aust. J. Chem. (1983) 36(12):2377-2386
5	$(H_2pic)[RuCl_2(pic)_2](Hpic)H_2O$	JD Gilbert, D Rose & G Wilkinson, J. Chem. Soc. (A) (1970):2765-9
6	$K[Ru(H_2edta)Cl_2]H_2O$	AA Diamantis & JV Dubrawski, Inorg. Chem. (1981) 20:1142-50
7	$K[Ru(hnta)_2]½H_2O$	MM Taqui Khan, A Kumar & Z Shirin, J. Chem. Research (M), (1986):1001-1009
8	$K[Ru(H_2dtpa)Cl]H_2O$	MM Taqui Khan, A Kumar & Z Shirin, J. Chem. Research (M), (1986):1001-1009
9	$[Ru_3O(lac)_6](lac)$	A Spencer & G Wilkinson, J. Chem. Soc. Dalton Trans (1972):1570-77
10	$[Ru_3O(OAc)_6](OAc)$	A Spencer & G Wilkinson, J. Chem. Soc. Dalton Trans (1972):1570-77
11	$[Ru_2(OAc)_4]NO_3$	M Mukaida, T Nomura & T Ishimori, Bull. Chem. Soc. Japan (1972) 45:2143-7
12	$[Ru_2(OCOEt)_4]NO_3$	A Bino, FA Cotton & TR Felthouse, Inorg. Chem. (1979) 18:2599-2604
13	$K_3[Ru(ox)_3]$	CM Che, SS Kwong, CK Poon, TF Lai & TCW Mak, Inorg. Chem. (1985) 24:1359-63
14	$[Ru_2(OAc)_4]Cl$	RW Mitchell, A Spencer & G Wilkinson, J. Chem. Soc. Dalton Trans. (1973) 846-54
15	$[Ru(NH_3)_5Cl]Cl_2$	AD Allen, F Bottomley, RO Harris, VP Reinsalu & CV Senoff, J. Amer. Chem. Soc. (1967) 89:5595-5599
16	$[Ru(en)_3]I_3$	TJ Meyer & H Taube, Inorg. Chem. (1968) 7:2369-2379
17	$K[RuCl_4(phen)]H_2O$	BR James & RS McMillan, Inorg. Nucl. Chem. Lett. (1975) 11(12):837-9
18	$[Ru(cyclam)Cl_2]Cl$	PK Chan, DA Isabirye & CK Poon, Inorg. Chem. (1975) 14:2579-80
19	$K[RuCl_4(bipy)]$	BR James & RS McMillan, Inorg. Nucl. Chem. Lett. (1975) 11(12):837-9
20	$[RuCl_3(dmso)_2(NH_3)]$	Patent: International Publication No. WO 91/13553
21	$[Ru(NH_3)_6]Cl_3$	Matthey Catalogue Sales: Cat No [190245]
22	$Cis\text{-}[RuCl_2(dmso)_4]$	EA Alessio, G Mestroni, G Nardin, WM Attia, M Calligaris, G Sava & S Zorget, Inorg. Chem. (1988) 27:4099-4106

Example	Compound	Literature Reference for Preparation
23	Cis-$[RuCl_2(dmso)_3(NH_3)]$	M Henn, E Alessio, G Mestrni, M Calligaris & WM Attia, Inorg. Chim. Acta (1991) 187:39-50
24	$[RuCl_3(dmso)_3]$	E Alessio, G Balducci, M Calligaris, G Costa, WM Attia & G Mestroni, Inorg. Chem. (1991) 30:609-618
25	$[Ru(mtc)_3]$	AR Hendrickson, JM Hope & RL Martin, J. Chem. Soc. Dalton Trans. (1976) 20:2032-9
26	$[Ru(maltol)_3]$	WP Griffith & SJ Greaves, Polyhedron (1988) 7(10):1973-9
27	$[Ru(acac)_2(MeCN)_2]CF_3SO_3$	Y Kasahara, T Hoshino, K Shimizu & GP Sato, Chem. Lett. (1990) 3:381-4
28	$K_2[RuCl_5(H_2O)]$	Matthey Catalogue Sales: Cat No [190094]
29	$[Os(ox)(bipy)_2]\cdot H_2O$	DA Buckingham, FP Dwyer, HA Goodwin & AM Sargeson, Aust. J. Chem. (1964) 325-336 GM Bryant, JE Fergusson & HKJ Powell, Aust. J. Chem. (1971) 24(2):257-73
30	$[Ru(NH_3)_4Cl_2]Cl$	SD Pell, MM Sherban, V Tramintano & MJ Clarke, Inorg Synth (1989) 26:65
31	[Ru(Hedtra)(dppm)]	MM Taqui Khan, K Venkatasubramanian, Z Shirin, MM Bhadbhade, J Chem Soc Dalt Trans (1992) 885-890
32	Ru(oep)Ph	M Ke, SJ Rettig, BR James & D Dolphin, J Chem Soc Chem Commun (1987) 1110

A number of new compounds were prepared according to the following protocols. The first four compounds are examples of rutheniuim complexes of formula $[Ru(H_{0-6}L^{II})_{1-3}Y_{0-2}Cl_{0-4}]^{(0-4)\pm}$ (Formula II), the subsequent two are examples of $[M_{1-3}Y_{1-8}Cl_{0-18}]^{(0-6)\pm}$ (formula III).

Preparation of $[Ru(Hhedtra)acac]\cdot H_2O$

Excess acetylacetone ($1cm^3$) was added to an aqueous solution ($5cm^3$) of K[Ru(hedtra)Cl] (0.5g). The solution color changed to violet. The mixture was warmed for 20 minutes then left to stand at room temperature for 20 minutes. The violet solution was extracted with chloroform ($20cm^3$). The extraction was repeated twice more. A violet product precipitated from the aqueous fraction. The product was filtered, washed in acetone and dried *in vacuo*, yield 0.1g (18%).

Anal. Calc. For $C_{15}H_{25}O_{10}N_2Ru$: C, 36.43; H, 5.11; N, 5.70. Found: C, 36.16; H, 5.42; N, 5.61%.

Preparation of [Ru(Hhedtra)trop]2H_2O

A three-fold excess of tropolone (0.78g) dissolved in 50:50 water/absolute ehtnaol (5cm^3) was added to a warm aqueous solution of K[Ru(hedtra)Cl] (10cm^3). The mixture was heated for 1 hour. On cooling, the dark green mixture was extracted with 3 x 20cm^3 portion sof dichloromethane. On standing, a dark green product precipitated from the aqueous fraction. The product was filtered, washed with water (1cm^3), ether and dried *in vacuo*, yield 0.4g (36%).

Anal. Cal. For $C_{17}H_{22}N_2O_9Ru \cdot 2H_2O$: C, 38.13; H, 4.86; N, 5.23. found: C, 38.55; H, 4.67; N, 5.28%.

Preparation of [Ru(H_3dtpa)Cl]

$K_2[RuCl_5H_2O] \cdot xH_2O$ (1g) was suspended in $HClO_4$ (15cm^3, 1mM) and diethylenetriaminepentaacetic acid (1.05g) added. The reaction mixture was heated under reflux for 1.5 hours forming a yellow/brown solution. On cooling a yellow product crystallised which was collected by filtration, washed with 90% absolute ethanol/water, diethyl ether and dried *in vacuo*, yield 0.75g, 53%.

Anal. calcd. for $C_{14}H_{21}N_3O_{10}ClRu$: C, 31.85; H, 3.98; N, 7.96; Cl, 6.73. Found: C, 29.77; H, 3.81; N, 7.36; Cl, 6.64.

Preparation of K[RuHHBEDCl]3H_2O

0.41g of $K_2[RuCl_5]xH_2O$ was dissolved in water (20ml). To this solution was added 1 equivalent (0.39g) of N,N'di(2-hydroxy-benzyl)ethylene-diamine N,N-diacetic acid (hbed) dissolved in water (50ml) with KOH (0.12g) and MeOH (1ml). This mixture was heated at reflux for 90 minutes. Upon cooling a dark, insoluble precipitate formed. This material was removed by filtration and the resulting red-violet solution was taken to dryness by rotary evapouration. Trituration with water and washing with acetone yilede 90mg of a dark solid.

Anal. Calcd. for $C_{18}H_{22}N_2O_9RuClK$: C, 36.89; H, 3.96; N, 4.78; Cl, 6.04. Found: C, 37.09; H, 4.23; N, 4.92; Cl, 6.28.

Preparation of $Ru(S_2CNCH_2CH_2NMeCH_2CH_2)_3½H_2O$

$Me_4N[S_2CNCH_2CH_2NMeCH_2CH_2]$ was made by the standard method and crystallised from methanol-ether in 71% yield.

$RuCl_3xH_2O$, 0.50g, 2.15mmol was refluxed in 30ml of methanol for 10 minutes and cooled. 1.87g, 7.50mmol of $Me_4N[S_2CNCH_2CH_2NMeCH_2CH_2]$ was added and the mixture refluxed for 16 hours. After cooling 0.72g of crude product was filtered off, dissolved in dichloromethane and filtered. The filtrate was loaded into 15cc of basic alumina and eluted with dichloromethane. Removal of solvent and crystallisation from dichloromethane with ether by vapour-phase diffusion gave 0.51g, 0.80mmol, 37% of brown-black crystals, $Ru(S_2CNCH_2CH_2NMeCH_2CH_2)_3½H_2O$.

Analysis for $C_{18}H_{34}N_6O_{.5}RuS_6$: Calc: C, 34.00; H, 5.39; N, 13.22; S, 30.25. Found: C, 34.21; H, 5.47; N, 13.12; S, 30.36.

Preparation of $Ru[S_2P(OC_2H_2OC_2H_4OMe)_2]_3$

$K[S_2P(OC_2H_4OC_2H_4OMe)_2]_3$ was made by standard method and crystallised from methanol in 76% yield.

$RuCl_3xH_2O$, 1.00g, 4.30mmol was refluxed in 50ml of 0.1 N HCl with 1ml of ethanol for 20 minutes and cooled. To this solution was added 5.28g (excess) $K[S_2P(OC_2H_4OC_2HROMe)_2]$ and the mixture stirred at 30°C for 1 hour. The reaction mixture was extracted with dichloromethane and the solvent removed. The residue was extracted with ether-hexane and solvents removed. This residue was crystallised from 25ml of hot ether by cooling to -20°C giving 2.98 of red crystals. 2.41g of the crude product was purified by chromatography on 60cc of silica gel with 5% ethanol in ether. The first band was collected, reduced to dryness and crystallised from ether by cooling to -20°C. The yield of red crystals, $Ru(S_2P[OC_2H_4OC_2H_4OMe]_2)_3$, was 2.16g, 56%.

Analysis for $C_{30}H_{66}O_{18}P_3RuS_6$: Calc: C, 32.72; H, 6.04; S, 17.47. Found: C, 32.68; H, 6.08; S, 17.16.

In the *in vitro* tests, which were carried out in an atmosphere of argon, each compound (1×10^4 moles) was dissolved in double-distilled deionized and deoxygenated water. The resulting solution was placed in a three-necked pear-shaped

flask and stirred by a magnetic stirrer at constant speed of 1000rpm, at a constant temperature in the range 20°C-24°C. A manometer was attached to the flask, and purified, dried nitric oxide gas (known volume in the range 3-5cm^3) was introduced via a septum, using a gas syringe, at atmospheric pressure into the headspace above the reaction solution. The pressure within the flask was recorded periodically over a period of one hour.

A control experiment was carried out according to the above but without any complex present.

The recorded pressures in association with the results of the control experiment were analysed in order to determine the rate of NO uptake as a function of time for each compound tested.

On completion of each *in vitro* test, the reaction solution was freeze-dried. An infrared spectrum of the freeze-dried product provided information on metal-NO bond formation.

In the *in vitro* cell culture tests, murine (RAW264) macrophage cell lines, which can be induced to produce nitric oxide, were seeded, 10^6 cells/well, onto 24 well culture plates of 2ml volume per well, in Eagles modified minimal essential medium (MEM) plus 10% fetal bovine serum without phenol red.

The cells were activated to produce nitric oxide, with 10μg/ml lipopolysaccharide and 100 units/ml interferon γ for 18 hours. Concurrently, test compounds made up in MEM were added at non-cytotoxic concentrations. Control cells as above, which were activated to produce nitric oxide as above, but to which no test compound was added, were used as a measure of the amouint of nitric oxide produced by the cells during the tests. (See S.P. Fricker, E. Slade, N. A. Powell, O. J. Vaughan, G. R. Henderson, B. A. Murrer, I. L. Megson, S. K. Bisland, F. W. Flitney, Ruthenium complexes as nitric oxide scavengers: a potential therapeutic approach to nitric oxide-mediated diseases, *Br. J. Pharmacol.*, 1997, 122, 1441-1449.)

Background nitric oxide was assessed by measurement of nitrate and nitrite in cells which were not activated.

Cell viability was confirmed by Trypan blue dye exclusion at the end of the incubation period.

Nitric oxide was determined by measurement of nitrate and nitrite in the cell supernatant. These anions are the stable end-products of reactions of NO in solution. Such reactions may or may not be catalysed in biological systems. The sum of nitrite and nitrate concentrations gives the total NO production. Nitrite was determined using the Griess reaction in which nitrite reacts with 1% sulphanilamide in 5% H_3PO_4/0.1% naphthylethylenediamine dihydrochloride to form a chromophore absorbing at 540nm. Nitrate was determined by reducing nitrate to nitrite with a bacterial nitrate reductase from *Pseudomonas oleovorans* and then measuring nitrite with the Griess reaction. In the absence of test compounds nitrite concentration plus nitrate concentration is equal to total nitric oxide production. The effect of test compounds on available nitric oxide (measured as nitrite + nitrate) was determined. The reduction in available nitric oxide compared with the control level may be taken as an indication of the degree of binding of NO by the test compounds.

In the *ex vivo* tests, segments of rat tail artery (0.8-1.5cm) were dissected free from normotensive adult Wistar rats. The arteries were internally perfused with Krebs solution (mM: NaCl 118, KCl 4.7, $NaHCO_3$ 25, NaH_2PO_4 1.15, $CaCl_2$ 2.5, $MgCl_2$ 1.1, glucose 5.6 and gassed with 95% O_2/5% CO_2 to maintain a pH of 7.4) in a constant flow perfusion apparatus. A differential pressure transducer located upstream of the vessel detected changes in back pressure. The rat tail artery preparation was pre-contracted with 6.5μM phenylephrine to give a physiologically normal pressure of 100-120mm Hg. The pre-contracted vessels were then perfused with the test compound. The arteries were perfused with Krebs solution between applications of test compound to wash out the test compound.

Pressure changes in the system served to indicate artery vasoconstriction. The vasoconstriction is a direct result of the removal of endogenous nitric oxide (edrf) from the endothelial cells of the rat tail artery.

RESULTS

The results of the *in vitro*, *in vitro* cell culture and *ex vivo* tests were as follows:

IN VITRO TESTS

EXAMPLE 1: $K[Ru(hedta)Cl]2H_2O$

A pressure decrease indicated binding of NO to the metal compound. This is illustrated in Figure 1.

The IR spectrum showed a peak at 1897cm^{-1}, indicating the presence of a Ru-NO bond.

EXAMPLE 2: $[Ru(H_2edta)(acac)]$

The IR spectrum showed a peak at 1896cm^{-1}, indicating the presence of a Ru-NO bond.

EXAMPLE 3: $K[Ru(hedtra)Cl]H_2O$

A pressure decrease indicated binding of NO to the metal compound. This is illustrated in Figure 1.

The IR spectrum showed a peak at 1889cm^{-1}, indicating the presence of a Ru-NO bond.

EXAMPLE 4: $K[Ru(dipic)_2H_2O$

A pressure decrease indicated binding of NO to the metal compound. This is illustrated in Figure 1.

The IR spectrum showed a peak at 1915cm^{-1}, indicating the presence of a Ru-NO bond.

EXAMPLE 5: $(H_2pic)[RuCl_2(pic)_2](Hpic)H_2O$

The IR spectrum showed a peak at 1888cm^{-1}, indicating the presence of a Ru-NO bond.

EXAMPLE 6: $K[Ru(H_2edta)Cl_2]H_2O$

A pressure decrease indicated binding of NO to the metal compound. This is illustrated in Figure 1.

The IR spectrum showed a peak at 1896cm^{-1}, indicating the presence of a Ru-NO bond.

EXAMPLE 7: $K[Ru(Hnta)_2]½H_2O$

A pressure decrease indicated binding of NO to the metal compound. This is illustrated in Figure 1.

The IR spectrum showed a peak at 1889cm^{-1}, indicating the presence of a Ru-NO bond.

EXAMPLE 8: $K[Ru(H_2dtpa)Cl]H_2O$

A pressure decrease indicated binding of NO to the metal compound. This is illustrated in Figure 1.

The IR spectrum showed a peak at 1905cm^{-1}, indicating the presence of a Ru-NO bond.

EXAMPLE 9: $[Ru_3O(lac)_6](lac)$

The IR spectrum showed a peak at 1884cm^{-1}, indicating the presence of a Ru-NO bond.

EXAMPLE 10: $[Ru_3O(OAc)_6](OAc)$

The IR spectrum showed a peak at 1877cm^{-1}, indicating the presence of a Ru-NO bond.

EXAMPLE 11: $[Ru_2(OAc)_4]NO_3$

The IR spectrum showed a peak at 1891cm^{-1}, indicating the presence of a Ru-NO bond.

EXAMPLE 12: $[Ru(OCOEt)_4]NO_3$

The IR spectrum showed a peak at 1891cm^{-1}, indicating the presence of a Ru-NO bond.

EXAMPLE 13: $K_3[Ru(ox)_3]$

The IR spectrum showed a peak at 1889cm^{-1}, indicating the presence of a Ru-NO bond.

EXAMPLE 14: $[Ru_2(OAc)_4]Cl$

The IR spectrum showed a peak at 1895cm^{-1}, indicating the presence of a Ru-NO bond.

EXAMPLE 15: $[Ru(NH_3)_5Cl]Cl_2$

The IR spectrum showed two peaks at 1909cm^{-1} and 1928cm^{-1}, indicating the presence of a Ru-NO bond.

EXAMPLE 16: $[Ru(en)_3]I_3$

The IR spectrum showed a peak at 1906cm^{-1}, indicating the presence of a Ru-NO bond.

EXAMPLE 17: $K[RuCl_4(phen)]H_2O$

The IR spectrum showed a peak at 1904cm^{-1}, indicating the presence of a Ru-NO bond.

EXAMPLE 18: $[Ru(cyclam)Cl_2]Cl$

The IR spectrum showed a peak at 1895cm^{-1}, indicating the presence of a Ru-NO bond.

EXAMPLE 19: $K[RuCl_4(bipy)]$

The IR spectrum showed a peak at 1885cm^{-1}, indicating the presence of a Ru-NO bond.

EXAMPLE 20: $[RuCl_3(dmso)_2(NH_3)]$

The IR spectrum showed a peak at 1889cm^{-1}, indicating the presence of a Ru-NO bond.

EXAMPLE 21: $[Ru(NH_3)_6]Cl_3$

The IR spectrum showed a peak at 1910cm^{-1}, indicating the presence of a Ru-NO bond.

EXAMPLE 22: cis-$[RuCl_2(dmso)_4]$

The IR spectrum showed a peak at 1881cm^{-1}, indicating the presence of a Ru-NO bond.

EXAMPLE 23: cis-$[RuCl_2(dmso)_3(NH_3)]$

The IR spectrum showed a peak at 1893cm^{-1}, indicating the presence of a Ru-NO bond.

EXAMPLE 24: $[RuCl_3(dmso)_3]$

The IR spectrum showed a peak at 1880cm^{-1}, indicating the presence of a Ru-NO bond.

EXAMPLE 25: $[Ru(mtc)_3]$

The IR spectrum showed a peak at 1862cm^{-1}, indicating the presence of a Ru-NO bond.

EXAMPLE 26: $[Ru(maltol)_3]$

The IR spectrum showed a peak at 1866cm^{-1}, indicating the presence of a Ru-NO bond.

EXAMPLE 27: $[Ru(acac)_2(MeCN)_2](CF_3SO_3)$

The IR spectrum showed a peak at 1899cm^{-1}, indicating the presence of a Ru-NO bond.

EXAMPLE 28: $K_2[RuCl_5(H_2O)]$

The IR spectrum showed a peak at 1903cm^{-1}, indicating the presence of a Ru-NO bond.

EXAMPLE 29: $[Os(ox)(bipy)_2]H_2O$

The IR spectrum showed a peak at 1894cm^{-1}, indicating the presence of a Ru-NO bond.

IN VITRO CELL CULTURE TESTS

Results are shown in Table 2 and Figure 2 for the *in vitro* cell culture tests using the compounds of Examples: 1-3, 6 14, 15 and 26, as follows.

EXAMPLE 1: $K[Ru(Hedta)Cl]2H_2O$

Available nitric oxide was reduced in a dose-dependent fashion with a maximum reduction of 75% at a concentration of 100μM.

EXAMPLE 2: $[Ru(H_2edta)(acac)]$

Available nitric oxide was reduced by 82% at 100μM test compound.

EXAMPLE 3: $K[Ru(Hedtra)Cl]H_2O$

Available nitric oxide was reduced by 42% at 100μM.

EXAMPLE 6: $K[Ru(H_2edta)Cl_2]H_2O$

Available nitric oxide was reduced by 77% at 100μM test compound.

EXAMPLE 14: $[Ru_2(OAc)_4]Cl$

Available nitric oxide was reduced by 47% at 100μM.

EXAMPLE 15: $[Ru(NH_3)_5Cl]Cl_2$

Available nitric oxide was reduced by 86% at 100μM test compound.

EXAMPLE 26: $[Ru(maltol)_3]$

Available nitric oxide was reduced by 71% at 100μM.

Table 2

		% Decrease of Available Nitric Oxide
Example 1	25μM	12
	50μM	23
	100μM	75
Example 2	100μM	82
Example 3	100μM	42
Example 6	100μM	77
Example 14	100μM	47
Example 15	100μM	86
Example 26	100μM	71

EX VIVO TESTS

Results are shown in Table 3 for the ex *vivo* tests using the compounds of Examples: 2, 3,14, 15 and 26, as follows.

EXAMPLE 2

Application of test compound resulted in a dose-dependent vasoconstriction at 10μM and 100μM. This effect was reversible by washout with Krebs solution.

EXAMPLE 14

Application of test compound resulted in a dose-dependent vasoconstriction at 10μM and 100μM. This effect was reversible by washout with Krebs solution.

EXAMPLE 15

Application of test compound resulted in a dose-dependent vasoconstriction at 10μM and 100μM. This effect was reversible by washout with Krebs solution.

EXAMPLE 26

Application of test compound resulted in a dose-dependent vasoconstriction at 10μM and 100μM and 1000μM. This effect was reversible by washout with Krebs solution.

Table 3

		% Vasoconstriction
Example 2	10μM	20
	100μM	69
Example 3	10μM	17
	100μM	59
Example 14	10μM	11
	100μM	40
Example 15	10μM	77
	100μM	86
Example 26	10μM	10
	100μM	18
	1000μM	25

Experimental

EXAMPLE 33

AMD7040: Synthesis of the Ru(III) complex of N,N'-[2,6-pyridylbis(methylene)]bis-iminodiacetic acid (pbbida)

N,N'-[2,6-pyridylbis(methylene)]bis-iminodiacetic acid ($Na_3Hpbbida$)

An aqueous solution of sodium hydroxide (30 mL, 0.01M), 2,6-dibromomethylpyridine·HBr (1.0 g, 2.9 mmol), iminodiacetic acid dimethyl ester (0.934 g, 5.8 mmol), and cetyltrimethylammonium bromide (0.21 g, 0.58 mmol) was stirred at room temperature for 3 days. A white precipitate formed which was removed by filtration and the filtrate was evaporated to give a white solid. This solid was purified by re-crystallisation from water and ethanol to give the desired compound as the tri-sodium salt (0.9 g, 71%). ^1H NMR (D_2O) δ 3.27 (s, 8H), 3.93 (s, 4H), 7.30 (d, 2H, J=7.5 Hz), 7.80 (t, 1H, J=7.8 Hz).

Preparation of [Ru(H_2pbbida)Cl]·2.5H_2O.

[Dihydrogen chloro[[2,6-(pyridinyl-κ*N*)methyl]bis[*N*-(carboxymethyl)glycinato-κ*N*,κ*O*]] ruthenium (III)]

Na_3Hpbbida (0.78 g, 1.8 mmol) was dissolved in HCl (20 mL, 1 mM) and the pH was adjusted to pH 4 with 1N HCl. $K_2[RuCl_5(OH_2)]$ (0.67 g, 1.8 mmol) dissolved in a minimum amount of aqueous HCl (1 mM) was added to the ligand solution and the resulting mixture was heated to reflux for 1.5 hours. A yellow precipitate formed throughout the course of the reaction. The reaction mixture was cooled in an ice bath and the yellow solid was collected via filtration, washed with ice cold water, ethanol and diethyl ether and then dried *in vacuo* at 70 °C for 2 hours (0.55 g, 56%). IR (CSI) ν(cm^{-1}) 1734(CO_2-) 1649(CO_2-) coordinated). Anal. Calcd. for $C_{15}H_{17}ClN_3O_8Ru·2.5H_2O$: C, 32.82; H, 4.04; N, 7.66; Cl, 6.47. Found: C, 32.82; H, 3.95; N 7.66; Cl, 6.47.

EXAMPLE 34

AMD7043: Synthesis of the Ru(III) complex of N,N'-bis[2-pyridyl(methylene)]ethylenediamine-N,N'-diacetic acid (H_2bped)

The ligand, H_2bped, was prepared according to literature procedures: See P. Caravan, S. J. Rettig, C. Orvig. *Inorg. Chem.* **1997**, *36*, 1306.

Preparation of [Ru(H_2bped)Cl_2]Cl.

[Dihydrogen dichloro[[*N*,*N*'-1,2-ethanediyl]bis[(2-pyridinyl-κ*N*)methylglycinato-κ*N*] ruthenium (III) chloride]

H_2bped·2HCl (1.0 g, 2.5 mmol) was dissolved in HCl (25 mL, 1 mM) and the pH was adjusted to pH 4 with 1N NaOH. A solution of $K_2[RuCl_5(OH_2)]$ in HCl (minimum volume, 1 mM) was added to the ligand solution and the reaction mixture was heated to reflux for 1.5 hours. The dark green solution was reduced to approximately one half the original volume and on slow evaporation a yellow-orange solid precipitated from the reaction mixture. This was collected by filtration and re-

crystallised from H_2O/EtOH to yield an orange micro-crystalline solid (0.37 g, 26%). IR (CSI) ν(cm^{-1})1726 (CO_2-). Anal. Calcd. for $C_{18}H_{22}Cl_3N_4O_4Ru$: C,38.21; H, 3.92; N, 9.90; Cl, 18.80. Found: C, 38.21; H, 3.96; N 9.90; Cl, 18.79.

EXAMPLE 35

AMD7056: Synthesis of the Ru(III) complex of N-[2-(2-pyridylcarboxamido)ethyl]iminodiacetic (pceida).

To a stirred solution of N-BOCethylenediamine (0.462 g) in dioxane (10 mL) was added picolinic acid hydroxysuccinimdyl ester (0.635 g) and the mixture was allowed to stir overnight. The reaction mixture was filtered and the filtrate was diluted with dichloromethane and washed with saturated aqueous sodium carbonate and then brine. The organic layer was dried (Na_2SO_4) and then evaporated to give a white solid (0.691 g, 90%). This was used without further purification.

The solid from above (0.691 g) was dissolved in pre-cooled (0 °C) trifluoroacetic acid (5 mL). The mixture was stirred for 2 hours at 0 °C and then room temperature for 15 minutes. The mixture was evaporated to dryness to give the pyridyl amine intermediate (~quantitative). The residue was dissolved in DMF (20 mL) with stirring and K_2CO_3 (1.8 g, 5.0 equiv.) followed by *t*-butyl bromoacetate (0.84 mL, 2.1 equiv.) were added and the reaction mixture was allowed to stir at room temperature for six days. The reaction mixture was diluted with water and extracted with ethyl acetate. The combined organic phases were then washed with brine and water, dried ($MgSO_4$) and evaporated to give the desired bis-*t*-butyl ester (1.02 g, 100%) as a light yellow oil. ^{1}H NMR ($CDCl_3$) δ 1.42 (s, 9H), 1.45 (s, 9H), 3.00 (t, 2H, *J*=6.1 Hz), 3.48 (s, 2H), 3.50-3.60 (m, 2H), 7.40 (m, 2H), 7.82 (dt, 1H, *J*=7.8, 1.6 Hz), 8.19 (d, 1H, *J*=7.8 Hz), 8.59 (d, 1H, *J*=4.6 Hz), 8.70 (br. m, 1H).

N-[2-(2-pyridylcarboxamido)ethyl]iminodiacetic·TFA salt (H_2pceida·TFA).

The di-*t*-butyl ester (1.02 g) from above was dissolved in dichloromethane (1 mL) and cooled to 0 °C. Pre-cooled trifluoroacetic acid was added (7 mL) and the solution was allowed to stir overnight at room temperature. The reaction mixture was then evaporated and the residue was dissolved in water (10 mL) and lyophilised to give the desired ligand (pceida) as a light yellow solid (0.71 g, 69%). ^{1}H NMR (D_2O)

δ 3.53 (t, 2H, *J*=5.7 Hz), 3.85 (t, 2H, *J*=5.7 Hz), 3.90 (s, 2H), 7.65 (m, 1H), 7.95-8.10 (m, 2H), 8.65 (s, 1H, *J*=4.8 Hz). Anal Calcd. for $C_{12}H_{15}N_3O_5 \cdot TFA \cdot H_2O$: C, 40.69; H, 4.39; N, 10.17. Found: C, 40.84; H, 4.32; N, 9.99.

Preparation of [Ru(pceida)(OH_2)Cl·1.5H_2O.

[Aquachloro[[*N*-2-[(2-pyridinyl-κ*N*)oxo-methyl)aminoethyl][((2-carboxy-κ*O*)methyl)glycinato-κ*N*,κ*O*]] ruthenium (III)]

H_2pceida·TFA (0.4 g, 1 mmol) and $K_2[RuCl_5(OH_2)]$ (0.38 g, 1 mmol) were dissolved in de-ionised water (10 mL) and the pH adjusted to pH5 with 1N NaOH. KCl (0.075 g, 1 mmol) was added to the reaction mixture and the solution was heated to reflux for 3 hours. The solution was cooled to room temperature and subsequently in an ice bath. Upon cooling a dark red-orange precipitate formed which was collected by filtration, washed with ice cold water and dried *in vacuo* at 40 °C overnight. Yield: 0.13 g, 29%. IR (CSI) ν(cm^{-1}) 1649(CO_2-). Anal. Calcd. for $C_{12}H_{15}ClN_3O_6Ru \cdot 1.5H_2O$: C, 31.28; H, 3.94; N, 9.12; Cl, 7.69. Found: C, 31.43; H, 3.92; N, 9.05; Cl, 7.80.

EXAMPLE 36

AMD7046: Synthesis of the Ru(III) complex of N-[2-pyridyl(methylene)]ethylenediamine-N,N',N'-triacetic acid (pedta).

To a solution of 2-pyridinecarboxaldehyde (3.2 g, 0.03 mol) in benzene (50 mL) was added N-BOC ethylenediamine (5.26 g, 1.1 equiv.) and the mixture was heated to reflux with stirring in a Dean-Stark apparatus for 1.5 hours. The reaction mixture was evaporated to dryness, dissolved in methanol (50 mL) and 5% palladium on carbon was added (0.5 g). The mixture was hydrogenated at 50 psi on a Parr apparatus overnight. The mixture was filtered through celite, and the filtrate was evaporated to give the pyridine intermediate (~ quantitative). ^{1}H NMR ($CDCl_3$) δ 1.40 (s, 9H), 2.75-2.85 (m, 2H), 3.20-3.35 (m, 2H), 3.90 (s, 2H), 5.30 (br. S, 1H), 7.10-7.20 (m, 1H), 7.30-7.36 (m, 1H), 7.60-7.70 (m, 1H), 8.50-8.60 (m, 1H).

To a stirred solution of the pyridine intermediate from above (5.08 g) in dichloromethane (30 mL) was added trifluoroacetic acid (30 mL) and the mixture was allowed to continue stirring overnight at room temperature. The mixture was evaporated to give a dark oil. ^{1}H NMR (d_6-DMSO/D_2O) δ 3.10-3.20 (m, 2H), 3.20-3.30 (m, 2H), 4.48 (s, 2H), 7.40-7.45 (m, 2H), 7.80-7.90 (m, 1H), 8.60 (m, 1H). This intermediate was used without further purification in the next step.

N-[2-pyridyl(methylene)]ethylenediamine-N,N',N'-triacetic acid tri-*t*-butyl ester.

To a solution of the oil from above in DMF (~80 mL) was added K_2CO_3 (27.9 g, 10.0 equiv.) followed by *t*-butylbromoacetate (8.95 mL, 3.0 equiv.) and the mixture was allowed to stir at room temperature for 48 hours. The reaction mixture was filtered through celite and the filtrate was evaporated to give a dark oil. Purification by column chromatography on silica gel (5% MeOH/ CH_2Cl_2) gave the tri-*t*-butyl ester (4.14 g, 42% for two steps) as a light yellow oil. ^{1}H NMR ($CDCl_3$) δ 1.35-1.50 (m, 27H), 2.83-2.86 (m, 4H), 3.37 (s, 2H), 3.43 (s, 4H), 3.95 (s, 2H), 7.10-7.20 (m, 1H), 7.52 (d, 1H, *J*=7.5 Hz), 7.64 (dt, 1H, *J*=7.5, 1.7 Hz), 8.51 (d, 1H, *J*=4.7 Hz).

N-[2-pyridyl(methylene)]ethylenediamine-N,N',N'-triacetic acid·TFA salt (pedta)

The tri-*t*-butyl ester from above (4.14 g) was dissolved in CH_2Cl_2 (20 mL) with stirring and trifluoroacetic acid (30 mL) was added in one portion. The mixture was allowed to stir at room temperature overnight and was then evaporated. The residue was dissolved in water (~40 mL) and charcoal (550 mg) was added. The mixture was heated to 70 °C and filtered through celite and the combined filtrates were then evaporated to small volume and lyophilised to give the desired ligand (pedta) as a yellow solid (3.24 g, 73%). ^{1}H NMR (D_2O) δ 3.00-3.15 (m, 2H), 3.20-3.30 (m, 2H), 3.59 (s, 4H), 4.04 (s, 2H), 4.51 (s, 2H), 7.50 (m, 1H), 7.61 (d, 1H, *J*=7.7 Hz), 7.98 (dt, 1H, *J*=7.7, 1.6 Hz), 8.63 (d, 1H, *J*=5.0 Hz). Anal. Calcd. for $C_{14}H_{19}N_3O_6$·1.8TFA: C, 39.83; H, 3.95; N, 7.92. Found: C, 38.85; H, 4.19; N, 8.06.

Preparation of [Ru(Hpedta)Cl]·0.5H_2O

[Hydrogen chloro[*N*-[bis((2-(carboxy-κ*O*)methyl)imino-κ*N*)ethyl]-(2-pyridinyl-κ*N*)methylglycinato-κ*N*] ruthenium (III)].

H_3pedta·TFA (0.75 g, 1.3 mmol) was dissolved in HCl (1.5 mL, 1 mM). A solution of $K_2[RuCl_5(OH_2)]$ (0.5 g, 1.3 mmol) in HCl (2 mL, 1 mM) was added to the ligand solution. The reaction mixture was heated to reflux for 2 hours and subsequently cooled to room temperature. An orange solid precipitated from the solution, which was collected by filtration, washed with ethanol and diethyl ether, and dried *in vacuo* at 40 °C overnight (0.26 g, 43%). IR (CSI) $\nu(cm^{-1})$ 1730(CO_2H); 1688, 1618 (CO_2-) coordinated). Anal. Calcd. for $C_{14}H_{17}ClN_3O_6Ru·0.5H_2O$: C 35.87; H 3.87; N 8.96; Cl 7.56. Found: C, 35.86; H, 3.79; N, 8.98; Cl, 7.58.

EXAMPLE 37

AMD7087: Synthesis of the Ru(III) complex of phenylenediamine-N,N,N',N'-tetraacetic acid (H_4pdta).

Phenylenediamine-N,N,N',N'-tetraacetic acid tetramethyl ester

1,2-phenylenediamine (1.4 g, 1.3 mmol), methyl bromoacetate (12.3 mL, 13 mmol) and K_2CO_3 (17.9 g, 13 mmol) were heated at 85 °C in DMF (130 mL) under an inert atmosphere for 3 days. The DMF was removed under reduced pressure and the residue was dissolved in CH_2Cl_2. The solution was washed with an aqueous solution of saturated NH_4Cl and then H_2O. The organic layer was dried ($MgSO_4$) and evaporated to give a brown oil. This brown oil was triturated with MeOH to yield a white solid, which was removed by filtration and washed with methanol (0.3 g, 5.8%). ^{1}H NMR ($CDCl_3$) δ 3.65 (s, 12H), 4.30 (s, 8H), 6.92-7.04 (m, 4H). FAB (+ve) *m/z* 397 $[M+H]^+$. Anal. Calcd. for $C_{18}H_{24}N_2O_8$: C, 54.54; H, 6.10; N, 7.07. Found: C, 54.57; H, 6.21; N, 7.19.

Phenylenediamine-N,N,N',N'-tetraacetic acid (H_4pdta)

The tetramethyl ester (0.1 g, 0.25mmol) was suspended in MeOH/H_2O (25 mL, 3/1) and cooled to 0 °C. Lithium hydroxide monohydrate (0.106 g, 2.5 mmol) was added to the suspension and the reaction mixture was stirred in the dark overnight (during which time it was allowed to warm to room temperature). The clear solution was acidified with HCl (2N) and the solvent was removed under reduced pressure to leave a white solid. ^{1}H NMR (D_2O/K_2CO_3) δ 4.27 (s, 8H), 7.25-7.4 (m, 4H). The white solid was used without further purification to prepare the ruthenium complex.

Preparation of $[Ru(Hpdta)(OH_2)]\cdot 3H_2O$

[Hydrogen aqua[*N*-bis((2-carboxy-κ*O*)methyl)imino-κ*N*]-1,2-phendiyl(2-(carboxy-κ*O*)methyl)glycinato-κ*N*] ruthenium (III)]

$H_4pdta\cdot xLiCl$ (0.25 mmol) was heated in HCl (3 mL, 1 mM) until completely dissolved. $K_2[RuCl_5(OH_2)]$ (0.095 g, 0.25 mmol) was added to the ligand solution and the reaction mixture was heated to reflux for 1.5 hours. The solution was allowed to cool to room temperature and the yellow-green precipitate which formed was collected by filtration and washed with H_2O, EtOH and Et_2O (15 mg, 12%). Anal. Calcd. for $C_{14}H_{15}N_2O_9Ru\cdot 3H_2O$: C, 32.95; H, 4.15; N, 5.49. Found: C, 32.65; H, 3.91; N, 5.58.

EXAMPLE 38.

AMD7459: Ruthenium (III) complex of N'-benzyldiethylenetriamine-N,N,N'',N''-tetraacetic acid (bdtta).

N-(hydroxyethyl)iminodiacetic acid di-t-butyl ester

Ethanolamine (1.84 g, 0.03 mol) was dissolved in dry THF (300 mL) and triethylamine (12.3 g, 0.12 mol) was added. To this stirring solution *t*-butylbromoacetate (23.5 g, 0.12 mol) was added and the reaction mixture was stirred for 16 hours. The solvent was removed *in vacuo* and the residue partitioned between Et_2O (100 mL) and H_2O (100 mL). The aqueous layer was extracted with Et_2O (3 x 100 mL), and the combined organic portions were dried over $MgSO_4$. The suspension was filtered and the solvent was removed *in vacuo* to afford the product (7.75 g, 89%) as a white solid. ^1H NMR ($CDCl_3$) δ 1.46 (6, 18H), 2.89 (t, 2H, J = 6.0 Hz), 3.45 (s, 4H), 3.53 (t, 2H, J = 6.0 Hz), 3.75 (bs, 1H). ^{13}C NMR ($CDCl_3$) δ 28.15, 56.68, 57.11, 59.37, 81.48, 171.48. ES-MS *m/z* 290 $[M+H]^+$.

N-[(Methanesulfonyl)ethyl]iminodiacetic acid di-t-butyl ester

N-(hydroxyethyl)iminodiacetic acid di-*t*-butyl ester (7.50 g, 0.03 mol) was dissolved in dry CH_2Cl_2 (250 mL) and triethylamine (14.8 g, 0.15 mol) was added. The solution was cooled in an ice bath and methanesulfonylchloride (3.55 g, 0.03 mol) was added dropwise with stirring. The reaction mixture was slowly warmed to

room temperature and stirred for a further 16 hours. The reaction was then quenched with *saturated* $NaHCO_3$ (150 mL) and the aqueous layer was extracted with CH_2Cl_2 (2 x 150 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and the solvent was removed *in vacuo* to afford the product (9.5 g, 99%) as an oil. ^1H NMR ($CDCl_3$) δ 1.46 (s, 18H), 3.08 (m, 5H), 3.48 (s, 4H), 4.34 (t, 2H, J = 6.0 Hz).

N'-benzyldiethylenetriamine-N,N,N",N"-tetraAcetic acid tetra-*t*-butyl ester

General Procedure A:

N-[(Methanesulfonyl)ethyl]iminodiacetic acid di-*t*-butyl ester (4.86 g, 13 mmol) was dissolved in dry acetonitrile (50 mL) and benzylamine (0.47 g, 4.4 mmol) was added with stirring. K_2CO_3 (2.4 g, 0.45 mol) was added and the suspension was stirred for 16 hours at 45°C. The solvent was removed *in vacuo* and the residue partitioned between $CHCl_3$ (100 mL) and *saturated* $NaHCO_3$ (100 mL). The aqueous portion was extracted with $CHCl_3$ (3 x 75 mL), and the combined organic extracts were dried ($MgSO_4$), filtered and the solvent was removed *in vacuo* to afford the crude product as a brown oil. The product was purified by column chromatography on silica gel (2% MeOH, 1% NEt_3, CH_2Cl_2) to afford the product (1.35 g, 37%) as a colorless oil. ^1H NMR ($CDCl_3$) δ 1.43 (s, 36H), 2.59 (t, 4H, J=6.0 Hz), 2.82 (t, 4H, J=6.0 Hz), 3.40 (s, 8H), 7.24 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 28.19, 52.08, 52.86, 56.16, 59.17, 80.75, 126.78, 128.14, 128.85, 139.62, 170.74. ES-MS *m/z* 650 $[M+H]^+$.

N'-benzyldiethylenetriamine-N,N,N",N"-tetraacetic acid·xTFA (bdtta)

General Procedure B:

N'-Benzyldiethylenetriamine-N,N,N",N"-tetracetic acid tetra-*t*-butyl ester (1.0 g, 1.5 mmol) was dissolved in trifluoroacetic acid (14.8 g, 130 mmol) and the solution was left stirring for 16 hours. The solvent was removed *in vacuo* and the residue was lyophilized to afford the product (1.19 g, 100%) as a white solid: ^1H NMR (D_2O) δ 3.38 (t, 4H, J = 6.0 Hz), 3.48 (t, 4H, J = 6.0 Hz), 3.73 (s, 8H), 4.43 (s, 4H), 7.51 (bs, 5H). ^{13}C NMR (D_2O) δ 50.22, 50.85, 55.43, 59.04, 129.50, 130.05, 130.90, 131.39, 172.64.

Preparation of [Ru(H$_2$bdtta)Cl]·4.5H$_2$O
[Dihydrogen chloro[[N,N'-[[(phenylmethyl)imino-κN]-2,1-ethanediyl]bis[N-(carboxymethyl)glycinato-κN,κO]] ruthenium (III)]

General Procedure C:

N'-Benzyldiethylenetriamine-N,N,N",N"-tetraacetic acid (bdtta) (0.256 g, 0.33 mmol) was dissolved in 1mM HCl (5 mL). $K_2[RuCl_5(H_2O)]$ (0.124 g, 0.33 mmol) was added and the reaction mixture was heated to 100 °C for 1.5 hours. The solution was then cooled and a yellow/green powder was collected. The powder was washed with the mother liquor, H_2O (2 x 10 mL), and Et_2O (3 x 5 mL) to afford the product (0.078 g, 24%) as a light yellow powder. Anal. Calcd. for $C_{19}H_{25}N_3O_8RuCl·4.5\ H_2O$: C, 35.60; H, 5.35; N, 6.56; Cl, 5.53. Found: C, 35.62; H, 5.22; N, 6.47; Cl, 5.33. IR (CsI) $\nu(cm^{-1})$ 1736 (CO_2H); 1657 (CO2-).

EXAMPLE 39

AMD7460: Ruthenium (III) complex of N'-[2-pyridyl(methylene)]diethylenetriamine-N,N,N",N"-tetraacetic acid (pdtta).

Using General Procedure A:

N-[(Methanesulfonyl)ethyl]iminodiacetic acid di-*t*-butyl ester (3.14 g, 8.5 mmol) was reacted with aminomethylpyridine (0.23 g, 2.0 mmol) and the crude reaction mixture was purified by silica gel chromatography (5% MeOH/ CH_2Cl_2). The product fractions were combined and partitioned between Et_2O (30 mL) and NaOH (15 mL 0.1M). The aqueous layer was extracted with Et_2O (3 x 20 mL), and the combined organic extracts were dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to afford the product (0.38 g, 30%) as an oil. ^1H NMR ($CDCl_3$) δ 1.40 (s, 36H), 2.64 (t, 4H, J = 6.0 Hz), 2.81 (t, 4H, J = 6.0 Hz), 3.38 (s, 8H), 3.76 (s, 2H), 7.08 (t, 1H, J = 6.0 Hz), 7.45 (d, 1H, J = 6.0 Hz), 7.57 (t, 1H, J = 6.0 Hz), 8.46 (d, 1H, 6.0 Hz). ^{13}C NMR ($CDCl_3$) δ 28.28, 52.17, 53.31, 56.14, 60.94, 121.74, 122.90, 136.32, 148.86, 160.25, 170.69. ES-MS *m/z* 651 $[M+H]^+$.

N'-[2-pyridyl(methylene)]diethylenetriamine-N,N,N",N"-tetraacetic acid·xHCl (pdtta)
Using General Procedure B:

The oil from above (0.381 g, 0.59 mmol) was treated with TFA (7.4 g, 65 mmol). The crude material was purified on Dowex cation exchange resin (H^+ form,

50W-200 mesh) to afford the product (0.225 g, 44%) as a white solid. ^{1}H NMR (D_2O) δ 3.09 (t, 4H, J = 6.6 Hz), 3.61 (t, 4H, J = 6.6 Hz), 3.86 (s, 2H), 4.20 (s, 8H), 7.97 (t, 1H, J = 6.9 Hz), 8.03 (d, 1H, J = 8.1 Hz), 8.53, (t, 1H, J = 8.1 Hz), 8.70 (d, 1H, J = 6.9 Hz).

Preparation of [Ru(H$_2$pdtta)Cl]·2H$_2$O
[Dihydrogen chloro[[N,N'-[[(2-pyridinylmethyl)imino-κN]di-2,1-ethanediyl]bis[N-(carboxymethyl)glycinato-κN,κO]]] ruthenium (III)].

Using General Procedure C:

Pdtta (0.225 g, 0.27 mmol) was reacted with $K_2[RuCl_5(H_2O)]$ (0.095 g, 0.25 mmol). Anal. Calcd. for $C_{18}H_{24}O_8N_4RuCl·2H_2O·1.0$ KCl·0.75HCl: C, 30.94; H, 4.15; N, 8.02; Cl, 13.95. Found: C, 30.85; H, 4.30; N, 8.01; Cl, 13.54. IR (CsI) ν(cm^{-1}) 1740 (CO_2H); 1657 (CO_2-); 311(Ru-Cl).

EXAMPLE 40.

AMD8676: Ruthenium (III) complex of N'-butyldiethylenetriamine-N,N,N'',N''-tetraacetic acid (budtta).

N'-butyldiethylenetriamine-N,N,N'',N''-tetraacetic acid tetra-t-butyl ester
Using General Procedure A:

N-[(Methanesulfonyl)ethyl]iminodiacetic acid di-*t*-butyl ester (2.97 g, 8.1 mmol) was reacted with butylamine (0.20 g, 3.0 mmol) and the crude reaction mixture was purified by silica gel chromatography (5% MeOH/CH_2Cl_2) to afford the product (0.439 g, 27%) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 0.81 (t, 3H, J = 6.0 Hz), 1.20 (m, 4H),1.38 (s, 36H), 2.38 (t, 2H, J = 7.5 Hz), 2.54 (t, 4H, J = 6.0 Hz), 2.71 (t, 4H, J = 6.0 Hz), 3.37 (s, 8H). ^{13}C NMR ($CDCl_3$) δ 14.36, 20.91, 28.49, 52.43, 53.61, 53.76, 54.92, 56.83, 81.31, 171.02. ES-MS *m/z* 616 $[M+H]^+$.

N'-butyldiethylenetriamine-N,N,N'',N''-tetraacetic acid·xTFA (budtta).
Using General Procedure B:

The oil from above (0.425 g, 0.69 mmol) was treated with TFA (14.8 g, 100 mmol) to afford the product (0.442 g, 87%) as an off-white solid. ^{1}H NMR (D_2O) δ 0.672 (bs, 3H), 0.81 (bs, 2H), 1.15 (bs, 2H), 2.71 (bs, 2H), 3.12 (bs, 8H), 3.56 (s, 8H). ES-MS *m/z* 448 $[M+H]^+$.

Preparation of [Ru(H$_2$budtta)Cl]·4H$_2$O

[Dihydrogen [[*N,N'*-[(butylimino-κ*N*)di-2,1-ethanediyl]bis[*N*-(carboxymethyl)glycinato-κ*N*,κ*O*]]]chloro ruthenium (III)].

Using General Procedure C:

Budtta (0.243 g, 0.33mmol) was reacted with $K_2[RuCl_5(H_2O)]$ (0.123 g, 0.33 mmol) to afford the product (0.083 g, 42%): Anal. Calcd. for $C_{16}H_{27}N_3O_8RuCl·4H_2O$: C, 32.14; H, 5.90; N, 7.03; Cl, 5.93. Found: C, 32.23; H, 5.60; N, 6.94; Cl, 6.02. IR (CsI) ν(cm^{-1}) 1736 (CO_2H); 1657 (CO_2-); 411(Ru-Cl).

EXAMPLE 41

AMD8679: Ruthenium (III) complex of N'-ethyldiethylenetriamine-N,N,N'',N''-tetraacetic acid (edtta).

N'-ethyldiethylenetriamine-N,N,N'',N''-tetraacetic acid tetra-*t*-butyl ester

Using General Procedure A:

N-[(Methanesulfonyl)ethyl]iminodiacetic acid di-*t*-butyl ester (3.169 g, 8.6 mmol) was reacted with ethylamine (0.13 g, 2.9 mmol) to afford, after purification by column chromatography on silica gel (2% MeOH, 1%NEt_3, CH_2Cl_2), the product (0.7 g, 55%) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 1.00 (t, 3H, *J* = 6.0 Hz), 1.46 (s, 36H), 2.56 (m, 6H), 2.80 (t, 4H, *J* = 7.5 Hz), 3.45 (s, 8H). ^{13}C NMR ($CDCl_3$) δ 28.17, 48.16, 52.10, 52.61, 53.44, 56.30, 80.77, 170.70. ES-MS *m/z* 588 $[M+H]^+$.

N'-ethyldiethylenetriamine-N,N,N'',N''-tetraacetic acid·xTFA (edtta)

Using General Procedure B:

The oil from above (0.591 g, 1.01 mmol) was treated with TFA (14.8 g, 100 mmol) to afford the product (0.699 g, 98%) as an off-white solid. ^{1}H NMR (D_2O) δ 0.92 (t, 3H, *J* = 6.9 Hz), 2.96 (d, 2H, *J* = 6.9 Hz), 3.24 (s, 8H), 3.69 (s, 8H). ^{13}C NMR (D_2O) δ 29.59, 49.19, 49.35, 49.95, 55.39, 170.68. ES-MS *m/z* 420 $[M+H]^+$.

Preparation of [Ru(H$_2$edtta)Cl]·H$_2$O

[Dihydrogen chloro[[*N,N'*-[(ethylimino-κ*N*)di-2,1-ethanediyl]bis[*N*-(carboxymethyl)glycinato-κ*N*,κ*O*]]] ruthenium (III)].

Using General Procedure C:

Reaction of edtta (0.241 g, 0.34 mmol) with $K_2[RuCl_5(H_2O)]$ (0.128 g, 0.34 mmol) afforded the product (0.0373 g, 21%). Anal. Calcd. for $C_{14}H_{23}N_3O_8RuCl \cdot 1H_2O \cdot 0.1KCl$: C, 32.13; H, 4.81; N, 8.03; Cl, 7.45. Found: C, 32.43; H, 4.80; N, 8.02; Cl, 7.81. IR (CsI) 1719 (CO_2H); 1678,1601(CO_2-); 415(Ru-Cl).

EXAMPLE 42:

AMD8684: Ruthenium (III) complex of N'-phenyldiethylenetriamine-N,N,N'',N''-tetraacetic acid (phdtta)

N'-phenyldiethylenetriamine-N,N,N''N''-tetraacetic acid tetra-t-butyl ester

Using General Procedure A:

Reaction of N-[(methanesulfonyl)ethyl]iminodiacetic acid di-*t*-butyl ester (3.358 g, 9.1 mmol) with aniline (0.28 g, 3.0 mmol) afforded, after purification by column chromatography on silica gel (4:1 Hexane: ethylacetate), the product (0.402 g, 21%) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 1.46 (s, 36H), 2.86 (t, 4H, J = 7.5 Hz), 3.47 (bs, 12H), 6.62 (t, 1H, J = 7.5 Hz), 6.70 (d, 1H, J = 9.0), 7.17 (t, 1H, J = 9.0 Hz).

N'-phenyldiethylenetriamine-N,N,N'',N''-tetraacetic acid·xTFA (phdtta)

Using General Procedure B:

The oil from above (0.281 g, 0.44 mmol) was reacted with TFA (7.4 g, 50 mmol) affording the product (0.272 g, 81%) as an off-white solid. ^{1}H NMR (D_2O) δ 3.21 (m, 4H), 3.67 (t, 4H, J = 6.6 Hz), 3.93 (s, 8H), 7.07 (t, 1H, J = 7.8 Hz), 7.08 (t, 1H, J = 7.8 Hz), 7.29 (t, 1H, J = 7.5 Hz).

Preparation of [Ru(H$_2$phdtta)Cl]·1.25H$_2$O

[Dihydrogen chloro[[N,N'-[(phenylimino-κN)di-2,1-ethanediyl]bis[N-(carboxymethyl)glycinato-κN,κO]]] ruthenium (III)].

Using General Procedure C:

Reaction of phdtta (0.146 g, 0.18 mmol) with $K_2[RuCl_5(H_2O)]$ (0.085 g, 0.23 mmol) afforded the product (0.0194 g, 16%). Anal. Calcd. for $C_{18}H_{23}N_3O_8RuCl \cdot 1.25H_2O \cdot 0.8KCl \cdot 0.8EtOH$: C, 35.40; H, 4.59; N, 6.32; Cl, 9.60. Found: C, 35.73; H, 4.47; N, 5.93; Cl, 9.79. IR (CsI) ν(cm^{-1}) 1730 (CO_2H); 1611 (CO_2-); 403(Ru-Cl)

EXAMPLE 43.

AMD7436: Ruthenium (III) complex of N,N''-bis-[2-pyridyl(methylene)] diethylenetriamine-N,N',N''-triacetic acid (bpdtta).

N,N',N''-Tritosyldiethylenetriamine

To a solution of tosyl chloride (21.18 g, 0.11 mol) in Et_2O (120 mL) was added diethylenetriamine (3.82 g, 0.04 mol). To this solution, an aqueous solution of NaOH (4.44 g, 0.11 mol) in de-ionized water (40 mL) was added dropwise. The resulting suspension was stirred for two hours and the white solid was collected by filtration and washed with H_2O and then Et_2O. The crude product was recrystallized from hot MeOH to afford the product (12.63 g, 60.4%) as a white crystalline solid. ^1H NMR ($CDCl_3$) δ 2.43 (bs, 9H), 3.06 (dt, 4H, J = 5.5, 6.9 Hz), 3.17 (t, 4H, J = 6.9 Hz), 6.55 (t, 2H, J = 5.5 Hz), 7.40 (m, 6H), 7.63 (d, 2H, J = 8.1 Hz), 7.74 (d, 4H, J = 8.1 Hz). ^{13}C NMR (acetone-d_6) δ 21.79, 43.51, 50.60, 128.26, 128.50, 130.92, 131.07, 137.27, 139.25, 144.38, 144.95. ES-MS *m/z* 588 $[M+H]^+$.

2-[Methanesulfonyl(methyl)]pyridine

2-Pyridinemethanol (3.39 g, 31.1 mmol) and triethylamine (9.44 g, 93 mmol) were dissolved in dry CH_2Cl_2 (250 mL) and the resulting solution was cooled to 0°C in an ice bath. Methanesulfonylchloride (4.27 g, 37.3 mmol) was added dropwise and the reaction mixture was stirred for 50 minutes. The reaction was then quenched with *saturated* $NaHCO_3$ (115 mL). The aqueous layer was washed with CH_2Cl_2 (2 x 50 mL), and the organic portions were combined and dried over $MgSO_4$. After filtering, the solvent was removed *in vacuo* to afford the product (6.5 g, 100%) as a red oil. ^1H NMR ($CDCl_3$) δ 3.11 (s, 3H), 5.33 (s, 2H), 7.30 (m, 1H), 7.48 (d, 1H, J = 7.8 Hz), 7.77 (dd, 1H, J = 1.7, 7.7 Hz), 8.59 (m, 1H).

N,N''-bis-[2-pyridyl(methylene)] –N,N',N''-tritosyldiethylenetriamine

To a solution of N,N',N''-tritosyldiethylenetriamine (8.8 g, 15.6 mmol) in DMF (75 mL) under a nitrogen atmosphere was added NaH (60% in oil, 1.24 g, 31.1 mmol) and the mixture was stirred for 45 minutes. 2-[Methanesulfonyl(methyl)]pyridine (6.5 g, 34.7 mmol) dissolved in 10 mL CH_2Cl_2 was then added and the reaction was heated to 80°C for 20 hours. Ethanol was then added and the DMF was removed *in vacuo*. The residue was dissolved in CH_2Cl_2 and washed with brine (3 x 100 mL), saturated NH_4Cl solution (3 x 100 mL), and finally a

saturated aqueous solution of K_2CO_3 (3 x 100 mL). The organic layer was dried over Na_2SO_4, filtered and the solvent was removed *in vacuo* to afford the crude product (9.0 g) as an off-white solid. ^1H NMR δ 2.42 (bs, 12H), 3.04 (m, 4H), 3.30 (m, 4H), 4.41 (s, 4H), 7.39 (m, 10H), 7.71 (m, 8H), 8.48 (m, 2H). ES-MS *m/z* 748 $[M+H]^+$. This product was used without further purification.

N,N''-bis-[2-pyridyl(methylene)]diethylenetriamine

The solid from above (3.79 g, 5.1 mmol) was added to 13 mL concentrated H_2SO_4 maintained at a temperature of 120°C. After 5 minutes the reaction mixture was cooled and EtOH (90 mL) was added resulting in the precipitation of a brown solid. The solid was collected by filtration, dissolved in H_2O (100 mL) and heated in the presence of activated charcoal. The mixture was filtered through celite and the volume of the filtrate was reduced to approximately 20 mL and then concentrated HCl (20 mL) was added. Most of the solvent was removed *in vacuo* and cold EtOH was added to precipitate a white solid. The white solid was then dissolved in H_2O and the pH was adjusted to 12 with 3M NaOH. The aqueous solution was extracted with $CHCl_3$ (3 x 50 mL), and the combined organic extracts were dried ($MgSO_4$). Evaporation of the solvent afforded the product (0.785 g, 54%) as a colorless oil. ^1H NMR δ 2.43 (s, 3H), 2.80 (s, 8H), 3.92 (s, 4H), 7.14 (t, 2H, J = 6.0 Hz), 7.30 (d, 2H, J = 6.0 Hz), 7.62 (dd, 2H, J = 3.0, 6.0 Hz), 8.53 (d, 2H, J = 3.0 Hz).

N,N''-bis-[2-pyridyl(methylene)]diethylenetriamine-N,N',N''-triacetic acid tri-*t*-butyl ester

The oil from above (0.737 g, 2.59 mmol) was dissolved in dry toluene (20 mL), containing *t*-butylbromoacetate (3.02 g, 15.50 mmol) and triethylamine (5.20 g, 51.0 mmol) and the reaction mixture was stirred overnight. After 16 hours the solvent was removed *in vacuo* and the residue was partitioned between Et_2O (40 mL) and H_2O (40 mL). The aqueous portion was extracted with Et_2O (2 x 40 mL) and the organic portions were combined, and dried over $MgSO_4$. Removal of the solvent *in vacuo* afforded the desired product (1.00 g, 62%) as an oil. ^1H NMR ($CDCl_3$) δ 1.40 (s, 9H), 1.45 (s, 18H), 2.75 (s, 8H), 3.27 (s, 2H), 3.32 (s, 4H), 3.91 (s, 4H), 7.12 (t, 2H, 6.0 Hz), 7.50 (d, 2H, 6.0 Hz), 7.62 (dd, 2H, J = 3.0, 6.0 Hz), 8.50 (d, 2H, J = 3 Hz). ES-MS *m/z* 628 $[M+H]^+$.

N,N''-bis[2-pyridyl(methylene)]diethylenetriamine-N,N',N''-triaceticacid·5TFA (bpdtta)

The oil from above (1.45 g, 2.30 mmol) was dissolved in trifluoroacetic acid (8.8 g, 78 mmol) and left stirring for 16 hours. The solvent was removed *in vacuo* and the resulting oil was lyophilized. An off-white powder was obtained (2.05 g, 86%). ^{1}H NMR (acetone-d_6) δ 3.50 (t, 4H, J = 5.7 Hz), 3.69 (s, 4H), 3.79 (t, 4H, J = 5.7 Hz), 4.41 (s, 2H), 4.53 (s, 4H), 8.04 (t, 2H, J = 6.4 Hz), 8.13 (d, 2H, J = 6.4 Hz), 8.59 (t, 2H, J = 7.9 Hz), 8.92 (d, 2H, J=7.9 Hz). ES-MS *m/z* 461 $[M+H]^+$. Anal. Calcd. for $C_{22}H_{29}N_5O_6$·5TFA·2.5H_2O: C, 35.77; H, 3.66; N, 6.34. Found: C, 35.54; H, 3.30; N, 6.18.

Preparation of $[Ru(H_2bpdtta)][CF_3CO_2]_2·3H_2O$

[*N*-[2-[[(carboxy-κ*O*)methyl][(2-pyridinyl-κ*N*)methyl]amino-κ*N*]ethyl-*N*-[2-[(carboxymethyl)[(2-pyridinyl-κ*N*]methyl]amino-κ*N*]ethyl]glycinato-κ*N*] ruthenium (III) bis(trifluoroacetate).

Bpdtta (0.37g, 0.35 mmol) was dissolved in 1mM HCl (3 mL) and the pH was adjusted to 4 with 1M NaOH. $K_2[RuCl_5(H_2O)]$ (0.13 g, 0.35 mmol), dissolved in a minimum amount of 1mM HCl was added to the reaction mixture. The solution was refluxed for 1.5 hours and then cooled in an ice bath. The residue was passed through Sephadex gel (G-10) and a yellow band was collected and lyophilized (0.11 g, 37%). Anal. Calcd. for $C_{22}H_{28}N_5O_6Ru$·2TFA·3H_2O: C, 37.19; H, 4.08; N, 8.34. Found: C, 37.16; H, 4.00; N, 8.62. IR (CsI) ν(cm^{-1}) 1688 (Co_2H); 1630(CO_2-).

EXAMPLE 44.

AMD8701: Ruthenium (III) complex of 1,3-Propanediamine-N,N,N',N'-tetraacetic acid (pdta).

1,3-Propanediamine-N,N,N',N'-tetraacetic acid tetra-t-butyl ester

1,3-propanediamine (0.528 g, 7.1 mmol) was dissolved in a mixture of dry THF (50 mL), triethylamine (5.76 g, 57 mmol) and *t*-butylbromoacetate (8.34 g, 43 mmol) and the reaction mixture was stirred under a nitrogen atmosphere for 24 hours.

The solvent was then removed *in vacuo* and the residue partitioned between $CHCl_3$ (40 mL) and *saturated* $NaHCO_3$ (30 mL). The aqueous portion was extracted with $CHCl_3$ (3 x 30 mL), and the combined organic portions were dried over $MgSO_4$, filtered, and the solvent removed *in vacuo*. The crude material was purified by silica gel chromatography (4:1 Hexanes: EtOAc) afforded the product (3.00 g, 80%) as a colorless oil. ^1H NMR ($CDCl_3$) δ 1.45 (s, 36H), 1.63-1.68 (m, 2H), 2.73 (dd, 4H, J = 6.0, 9.0 Hz), 3.42 (s, 8H). ^{13}C NMR δ 28.18, 51.93, 55.76, 80.80, 170.74. ES-MS *m/z* 531 $[M+H]^+$.

1,3-Propanediamine-N,N,N',N'-tetraacetic acid·xTFA (pdta)

Using General Procedure B:

Reaction of the oil from above (0.866 g, 1.63 mmol) with TFA (8.88 g, 78 mmol) afforded the product (0.8405 g, 96%). ^1H NMR (CD_3OD) δ 2.15-2.19 (m, 2H), 3.43 (t, 4H, J = 6.0 Hz), 4.16 (s, 8H). ES-MS *m/z* 307 $[M+H]^+$.

Preparation of $K[Ru(H_2pdta)Cl_2]\cdot 3H_2O$

[Potassium dihydrogen dichloro[[*N,N'*-1,3-propanediylbis[*N*-(carboxymethyl)glycinato-κ*N*,κ*O*]]] ruthenium (III)]

Using General Procedure C:

Reaction of pdta (0.291 g, 0.54 mmol) with $K_2[RuCl_5(H_2O)]$ (0.203 g, 0.54 mmol) afforded the product (0.075 g, 24%) as a yellow solid. Anal. Calcd. for $C_{11}H_{16}N_2O_8\ Cl_2RuK\cdot 3.0H_2O$: C, 23.20; H, 3.89; N, 4.92; Cl, 12.45. Found: C, 22.97; H, 3.67; N, 4.80; Cl, 12.15. IR (CsI) ν (cm^{-1}) 1738 (CO_2H); 1642 (CO_2-); 316(Ru-Cl).

EXAMPLE 45.

AMD7494: Ruthenium (III) complex of N-[2-(carboxy)-6-pyridyl(methylene)]iminodiacetic acid (cpida).

Methyl 2-(hydroxymethyl)pyridinecarboxylate

Dimethyl-2,6-pyridinedicarboxylate (1.057 g, 5.4 mmol) was dissolved in dry CH_2Cl_2 (45 mL) and the solution was cooled to –78°C. DIBAL-H (11 mL, 10.8 mmol) was added dropwise with stirring and the solution was stirred at –78°C for 0.5

hours and then slowly warmed to room temperature over a period of 1 hour. The reaction was quenched with H_2O (15 mL) /sodium potassium tartrate (15 mL) and extracted with CH_2Cl_2 (3 x 80 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated *in vacuo* to afford the crude product. Purification by column chromatography on silica gel (4:1 Hexanes : Ethyl acetate to 10% MeOH/ CH_2Cl_2) afforded the desired product (0.220 g, 26%) as a colorless oil. ^1H NMR ($CDCl_3$) δ 3.33 (t, 1H, J = 4.5 Hz), 4.00 (s, 3H), 4.87 (d, 2H, J = 4.5 Hz), 7.54 (d, 1H, J = 6.0), 7.83 (dd, 1H, J = 6.0, 9.0), 8.00 (d, 1H, J = 9.0 Hz).

Methyl 2-(methanesulfonylmethyl)pyridinecarboxylate

To a stirred solution of methyl 2-(hydroxymethyl)pyridinecarboxylate (0.220 g, 1.3 mmol) dissolved in dry CH_2Cl_2 (13 mL) and triethylamine (0.40 g, 4.0 mmol) cooled in an ice bath was added dropwise, methanesulfonylchloride (0.18 g, 1.6 mmol). After 30 minutes the reaction was quenched with *saturated* $NaHCO_3$ (15 mL) and the aqueous phase was separated and extracted with CH_2Cl_2 (3 x 15 mL). The combined organic extracts were dried ($MgSO_4$) and the solvent was evaporated *in vacuo* to afford the product (0.347g, 100%) as a yellow orange oil. ^1H NMR ($CDCl_3$) δ 3.15 (s, 3H), 4.01 (s, 3H), 5.44 (s, 2H), 7.70 (d, 1H, J = 6.0 Hz), 7.92 (dd, 1H, J = 6.0, 9.0 Hz), 8.12 (d, 1H, J = 9.0 Hz).

N-[2-(carboxymethyl)-6-pyridyl(methylene)]iminodiacetic acid dimethyl ester

General Procedure D:

The oil from above (0.323 g, 1.3 mmol) was dissolved in dry DMF (13 mL) and iminodiacetic acid dimethyl ester (0.191 g, 1.2 mmol) was added. Once the reagents had dissolved, K_2CO_3 (0.36 g, 2.6 mmol) was added and the reaction mixture was stirred at 35 °C for 16 hours. The solvent was removed *in vacuo* and partitioned between H_2O (10 mL) and CH_2Cl_2 (15 mL) . The aqueous portion was extracted with CH_2Cl_2 (3 x 15 mL), and the combined organic extracts were dried ($MgSO_4$) and evaporated *in vacuo* . The crude material was purified by silica gel chromatography (75% EtOAc/hexanes) to afford the product (0.200 g, 49%) as a colorless oil. ^1H NMR ($CDCl_3$) δ 3.70 (s, 6H), 3.97 (s, 3H), 4.16 (s, 4H), 5.36 (s, 2H), 7.51 (d, 1H, J = 9.0), 7.84 (dd, 1H, J = 6.0, 9.0), 8.02 (d, 1H, J = 6.0 Hz). ^{13}C NMR δ 49.48, 52.63, 53.32, 68.46, 124.46, 124.79, 138.25, 155.93, 157.31, 165.88, 170.09.

N-[2-(carboxy)-6-pyridyl(methylene)]iminodiacetic acid·xHCl (cpida)

The oil from above (0.200 g, 0.65 mmol) was dissolved in MeOH (19 mL) and H_2O (6 mL) and the solution was cooled to 0 °C using an ice bath. Lithium hydroxide monohydrate (0.270 g, 6.4 mmol) was added and the mixture was stirred for 17 hours at room temperature in the absence of light. The solution was acidified with 2N HCl and the solvent was removed *in vacuo*. The crude material was purified on Dowex cation exchange resin (H^+form, 50W-200 mesh) to afford the product (0.172 g, 78%). ^1H NMR (D_2O) δ 4.02 (s, 2H), 4.15 (s, 2H), 5.39 (s, 2H), 7.95 (d, 1H, J = 7.5 Hz), 8.25 (d, 1H, J = 7.2 Hz), 8.46 (dd, 1H, J = 7.2, 7.5 Hz). ^{13}C NMR (D_2O) δ 50.27, 50.56, 127.02, 128.74, 147.29, 152.83, 156.73, 173.22, 173.46. ES-MS *m/z* 313 $[M+H]^+$.

Preparation of [Ru(Hcpida)(OH$_2$)(Cl)]·1.5H$_2$O

[Hydrogen aqua[6-[[[(carboxy-κ*O*)methyl](carboxymethyl)amino-κ*N*]methyl]-2-pyridinecarboxylato-κN^1,κO^2]chloro ruthenium (III)].

Using General Procedure C:

Reaction of cpida (0.157 g, 0.48 mmol) with $K_2[RuCl_5(H_2O)]$ (0.172 g, 0.46 mmol) afforded the product. Anal. Calcd. for $C_{11}H_{12}N_2O_7RuCl·1.5H_2O·0.9KCl$: C, 25.66; H, 2.94; N, 5.44; Cl, 13.08. Found: C, 25.56; H, 2.64; N, 5.06; Cl, 12.97. IR (CsI): ν(cm^{-1}) 1709 (CO2H); 1632, 607(CO_2-); 341(Ru-Cl).

EXAMPLE 46.

AMD7493: Ruthenium (III) complex of N-[2-(Hydroxymethyl)-6-pyridyl(methylene)]iminodiacetic acid (hpida).

2-[Methanesulfonyl(methylene)]-6-pyridinecarboxaldehyde

2-(Hydroxymethyl)-6-pyridinecarboxaldehyde (2.30 g, 0.017 mol) was dissolved in dry CH_2Cl_2 (160 mL) containing triethylamine (5.08 g, 0.05 mol). The solution was cooled to 0 °C in an ice bath and methanesulfonylchloride (2.12 g, 0.018 mol) was added dropwise. Stirring was continued for 0.5 hours and the reaction was quenched with *saturated* $NaHCO_3$ (160 mL). The aqueous portion was extracted with CH_2Cl_2 (3 x 150 mL), and the combined organic extracts were dried (Na_2SO_4) and the solvent was removed *in vacuo* to afford the product (3.61 g, 100%) as a brown oil. ^1H

NMR ($CDCl_3$) δ 3.15 (s, 3H), 5.43 (s, 2H), 7.70 (m, 1H), 7.97 (m, 2H), 10.05 (s, 1H). This was used without further purification.

Using General Procedure D.

Reaction of the oil from above (3.61 g, 0.017 mol) with iminodiaceticacid di-*t*-butyl ester (3.706 g, 0.015mmol) afforded, after column chromatography on silica (4:1 hexanes: EtOAc), the product (2.136 g, 40%) as a colorless oil. ^1H NMR ($CDCl_3$) δ 1.46 (s, 18H), 3.50 (s, 4H), 4.14 (s, 2H), 7.85 (m, 1H), 7.94 (m, 1H), 10.05 (s, 1H).

N-[2-(Hydroxymethyl)-6-pyridyl(methylene)]iminodiacetic acid di-*t*-butyl ester.

The oil from above (2.25 g, 6.2 mmol) was dissolved in dry MeOH (60 mL) under a nitrogen atmosphere. Sodium borohydride (0.235 g, 6.2 mmol) was added in one portion and the reaction was heated to 60 °C with stirring. After 1 hour the solvent was removed *in vacuo* and the residue was partitioned between H_2O (30 mL) and CH_2Cl_2 (30 mL). The aqueous phase was separated and extracted with CH_2Cl_2 (3 x 40 mL) and the combined organic extracts were dried ($MgSO_4$) and evaporated *in vacuo* to afford the product (2.16 g, 95%) as a colorless oil. ^1H NMR ($CDCl_3$) δ 1.46 (s, 18H), 3.48 (s, 4H), 3.98 (t, 1H, J = 4.5 Hz), 4.05 (s, 2H), 4.72 (d, 2H, J = 4.5 Hz), 7.08 (d, 1H, J = 6.0 Hz), 7.53 (d, 1H, J = 9.0 Hz), 7.66 (dd, 1H, J = 6.0, 9.0 Hz). ^{13}C NMR ($CDCl_3$) δ 28.57, 56.22, 59.88, 64.13, 81.47, 119.04, 122.02, 137.64, 158.25, 158.65, 170.90. ES-MS *m/z* 367 $[M+H]^+$.

N-[2-(Hydroxymethyl)-6-pyridyl(methylene)]iminodiacetic acid.xTFA (hpida)

Using General Procedure B:

Reaction of N-[2-(Hydroxymethyl)-6-pyridyl(methylene)]iminodiacetic acid di-*t*-butyl ester with TFA (4.44 g, 40 mmol) afforded the product (0.492 g, 100%) as a white solid. ^1H NMR (D_2O) δ 3.64 (s, 4H), 4.28 (s, 2H), 4.85 (s, 2H), 7.69 (bs, 2H), 8.27 (t, 1H, J = 8.0 Hz). ^{13}C NMR (D_2O) δ 55.98, 60.07, 123.75, 125.19, 147.02, 152.72, 155.65, 174.85. ES-MS *m/z* 255 $[M+H]^+$.

Preparation of [Ru(Hhpida)(OH_2)Cl_2]·H_2O

[Hydrogen aqua[*N*-(carboxymethyl)-*N*-[[6-(hydroxymethyl)-2-pyridinyl-κ*N*]methyl]glycinato-κ*N*,κ*O*]dichloro ruthenium (III)].

Following General Procedure C:

Reaction of hpida (0.152 g, 0.32 mmol) with $K_2[RuCl_5(H_2O)]$ (0.118 g, 0.32 mmol) afforded the product (0.0352 g, 24%). Anal. Calcd. for $C_{11}H_{15}N_2O_6Cl_2Ru{\cdot}H_2O$: C, 28.64; H, 3.71; N, 6.07; Cl, 15.37. Found: C, 28.44; H, 3.67; N, 6.02; Cl, 15.36. IR (CsI) $\nu(cm^{-1})$ 1657, 1630(CO_2-); 316(Ru-Cl).

EXAMPLE 47.

AMD8699: Ruthenium (III) complex of N-[2-(benzyloxymethyl)-6-pyridyl(methylene)]iminodiacetic acid (bpida).

2-(Benzyloxymethyl)-6-(hydroxymethyl)pyridine

2,6-Pyridinedimethanol (1.523 g, 0.011 mol) was dissolved in DMSO (5 mL) and powdered KOH (0.63 g, 0.011 mol) was added. After 10 minutes benzylbromide (1.87 g, 0.011 mol) was added and the reaction was heated to 80 °C for 17 hours. The reaction mixture was quenched with H_2O (9 mL) and extracted with Et_2O (3 x 25 mL). The combined organic extracts were dried ($MgSO_4$) and the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography on silica (1:1 hexanes: EtOAc and then EtOAc) to afford the product (0.971g, 39%) as a colorless oil. ^1H NMR ($CDCl_3$) δ 3.79 (bs, 1H), 4.66 (s, 2H), 4.70 (s, 2H), 7.48 (d, 2H, J = 3.6 Hz), 7.13 (d, 1H, J = 7.5 Hz), 7.32-7.43 (m, 6H), 7.70 (dd, 1H, J = 7.2, 7.8 Hz). ^{13}C NMR ($CDCl_3$) δ 60.40, 63.89, 72.96, 119.01, 119.91, 127.80, 128.48, 137.31, 137.94, 157.57, 158.16.

2-(Benzyloxymethyl)-6-(methanesulfonylmethyl)pyridine

The oil from above (0.971 g, 4.24 mmol) was dissolved in dry CH_2Cl_2 (40 mL) containing triethylamine (1.29 g, 12.7 mmol) under a nitrogen atmosphere and the solution was cooled to 0°C with stirring in an ice bath. Methanesulfonylchloride (0.577 g, 5.0 mmol) was then added dropwise and the mixture was stirred for 45 minutes and then quenched with *saturated* $NaHCO_3$ (30 mL). The separated aqueous phase was extracted with CH_2Cl_2 (2 x 20 mL) and the combined organic extracts were dried ($MgSO_4$) and evaporated *in vacuo* to afford the product (1.18g, 91%) as a brown

oil. ^{1}H NMR ($CDCl_3$) δ 3.07 (s, 3H), 4.65 (s, 2H), 4.67 (s, 2H), 5.29 (s, 2H), 7.27-7.38 (m, 6H), 7.50 (d, 1H, J = 9.0 Hz), 7.77 (dd, 1H, J = 6.0, 9.0 Hz).

N-[2-(benzyloxymethyl)-6-pyridyl(methylene)]iminodiaceticacid di-*t*-butyl ester

Using General Procedure D:

Reaction of the oil from above (1.18 g, 3.84mmol) with iminodiacetic acid di-*t*-butyl ester (0.85 g, 3.47 mmol) afforded, after silica gel chromatography (4:1 Hexanes: EtOAc), the product (0.772 g, 45%) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 1.45 (s, 18H), 3.48 (s, 4H), 4.03 (s, 2H), 4.65 (s, 2H), 4.67 (s, 2H), 7.27-7.38 (m, 6H), 7.54 (d, 1H, J = 7.5 Hz), 7.68 (dd, 1H, J = 7.5, 7.8 Hz). ^{13}C NMR ($CDCl_3$) δ 28.19, 55.78, 59.83, 72.92, 73.26, 80.98, 119.58, 121.46, 127.71, 127.83, 128.42, 137.16, 138.09, 157.82, 158.86, 170.53. ES-MS *m/z* 457 $[M+H]^+$.

N-[2-(benzyloxymethyl)-6-pyridyl(methylene)]iminodiacetic acid·xTFA (bpida).

Using General Procedure B:

Reaction of the product from above (0.7 g, 1.53 mmol) with TFA (10.36 g, 90 mmol) afforded the product (0.876 g, 100%) as a yellow viscous oil. ^{1}H NMR (D_2O) δ 3.77 (s, 4H), 4.44 (s, 2H), 4.75 (s, 2H), 4.92 (s, 2H), 7.33-7.41 (m, 5H), 7.76 (d, 1H, J = 9.0 Hz), 7.83 (d, 1H, J = 6.0 Hz), 8.33 (dd, 1H, J = 6.0, 9.0 Hz). ^{13}C NMR (D_2O) δ 55.73, 56.51, 67.68, 68.27, 73.62, 123.45, 124.33, 128.18, 128.58, 137.52, 144.88, 154.30, 172.94. ES-MS *m/z* 345 $[M+H]^+$.

Preparation of [Ru(bpida)Cl(OH$_2$)]

[Aqua[*N*-[(carboxy-κ*O*)methyl]-*N*-[[6-[(phenylmethoxy)methyl]-2-pyridinyl-κ*N*]methyl]glycinato-κ*N*,κ*O*]chloro ruthenium (III)]

Using General Procedure C:

Reaction of bpida (0.376 g, 0.66 mmol) with $K_2[RuCl_5(H_2O)]$ (0.247 g, 0.66 mmol) afforded the product (0.0910 g, 26%) as a yellow solid. Anal. Calcd. for $C_{18}H_{20}N_2O_6RuCl·0.4KCl$: C, 41.05; H, 3.83; N, 5.32; Cl, 9.42. Found: C, 41.30; H, 3.95; N, 5.27; Cl, 9.83. IR (CsI) ν(cm^{-1}) 1657(CO_2-); 391(Ru-Cl).

EXAMPLE 48.

AMD8677: Ruthenium (III) complex of N-[(3-carboxymethyl)benzyl]ethylenediamine-N,N',N'-triacetic acid (cmbedta).

Ethylenediamine-N,N',N'-triacetic acid tri-t-butyl ester

To a stirred solution of ethylenediamine (0.50 g, 8.3 mmol) in dry THF (70 mL) and triethylamine (3.34 g, 33 mmol) was added *t*-butylbromoacetate (4.9 g, 25 mmol) and the reaction mixture was stirred for 16 hours at room temperature. The solvent was removed *in vacuo* and the residue was partitioned between CH_2Cl_2 (80 mL) and H_2O (50 mL). The separated aqueous phase was extracted with CH_2Cl_2 (2 x 80 mL) and the combined organic extracts were dried ($MgSO_4$) and evaporated *in vacuo*. The crude material was purified by column chromatography on silica gel (5% MeOH / CH_2Cl_2) to afford the product (0.887g, 27%) as an oil. ^1H NMR ($CDCl_3$) δ 1.43 (s, 27H), 2.63 (t, 2H, J = 6.0 Hz), 2.84 (t, 2H, J = 6.0 Hz), 3.28 (s, 2H), 3.42 (s, 4H). ^{13}C NMR ($CDCl_3$) δ 28.46, 28.51, 47.42,51.84, 54.15, 56.41, 81.31, 81.36, 171.22, 171.68.

N-[(3-carboxymethyl)benzyl]ethylenediamine-N,N',N'-triacetic acid tri-*t*-butyl ester

General Procedure E:

To a stirred solution of the oil from above (0.165 g, 0.41 mmol) in dry THF (5 mL) and triethylamine (0.087 g, 0.86 mmol) was added 3-bromomethylbenzoate (0.094 g, 0.41 mmol) and the reaction was stirred at 35 °C for 22 hours. The solvent was removed *in vacuo* and the residue was partitioned between CH_2Cl_2 (10 mL) and *saturated* $NaHCO_3$ (10 mL). The separated aqueous phase was extracted with CH_2Cl_2 (2 x 10 mL), and the combined organic extracts were dried ($MgSO_4$) and evaporated *in vacuo*. The crude material was purified by radial chromatography on silica gel (7:1 Hexanes:EtOAc) to afford the product (0.115 g, 51%) as a colorless oil. ^1H NMR ($CDCl_3$) δ 1.40 (s, 18H), 1.43 (s, 9H), 2.79-2.86 (m, 4H), 3.25 (s, 2H), 3.40 (s, 4H), 3.83 (s, 2H), 3.87 (s, 3H), 7.35 (dd, 1H, J = 6.0, 9.0 Hz), 7.55 (d, 1H, J = 9.0 Hz), 7.89 (d, 1H, J = 6.0 Hz), 7.95 (s, 1H).

N-[(3-carboxymethyl)benzyl]ethylenediamine-N,N',N'-triacetic acid·xTFA (cmbedta)

Using General Procedure B:

Reaction of the oil from above (0.115 g, 0.21 mmol) with TFA (7.4 g, 65 mmol) afforded the product (0.094 g, 74%) as a light brown solid. ^1H NMR (D_2O) δ

3.16 (bs, 2H), 3.43-3.48 (m, 6H), 3.90 (s, 3H), 4.09 (s, 2H), 4.63 (s, 2H), 7.58 (t, 1H, J = 7.8 Hz), 7.83 (d, 1H, J = 7.8 Hz), 8.10 (d, 1H, J = 7.8 Hz), 8.23 (s, 1H). ^{13}C NMR (D_2O) δ 50.93, 53.38, 54.09, 54.53, 56.27, 60.46, 131.15, 132.48, 132.59, 132.78, 133.58, 137.21, 168.28, 169.47, 175.47.

Preparation of K[Ru(cmbedta)Cl]·H_2O

[Potassium chloro[methyl 3-[[[2-[bis[(carboxy-κ*O*)methyl]amino-κ*N*]ethyl][(carboxy-κ*O*)methyl]amino-κ*N*]methyl]benzoato ruthenium (III)].

Using General Procedure C:

Reaction of cmbedta (0.094 g, 0.16 mmol) with $K_2[RuCl_5(H_2O)]$ (0.058 g, 0.16 mmol) afforded the product (0.0334 g, 36%) as a yellow solid. Anal. Calcd. for $C_{17}H_{19}N_2O_8RuClK·0.15KCl·H_2O$: C, 34.95; H, 3.62; N, 4.80; Cl, 6.98. Found: C, 35.19; H, 3.92; N, 4.80; Cl, 7.28. IR (CsI) ν (cm^{-1}) 1728 (CO_2Me); 1686(CO_2-); 386(Ru-Cl).

EXAMPLE 49.

AMD8893: Ruthenium (III) Complex of N-[2-(N-acetylpyrrolidine)]ethylenediamine-N,N',N'-triacetic acid (apedta).

Chloroacetylpyrrolidine

A solution of chloroacetyl chloride (3.6 mL, 45.0 mmol) in anhydrous THF (10 mL) was added dropwise to a stirred mixture of pyrrolidine (2.56 g, 36.0 mmol) and potassium carbonate (7.46 g, 54.0 mmol) in anhydrous THF (50 mL) cooled to 0 °C. The reaction mixture was stirred at 0 °C for 30 minutes and the reaction mixture was then evaporated to give a white solid. The solid was partitioned between CH_2Cl_2 and H_2O and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic phases were washed twice with H_2O, twice with NH_4Cl (1 N) then dried ($MgSO_4$) and evaporated to give a yellow oil (2.97 g, 55.9%). ^{1}H NMR ($CDCl_3$) δ 1.84 (m, 2H), 2.02 (m, 2H), 3.52 (q, 4H, J=6.0 Hz), 4.02 (s, 2H).

N-[2-(N-acetylpyrrolidine)]ethylenediamine-N,N',N'-triacetic acid tri-*t*-butyl ester

Potassium carbonate (0.69 g, 4.98 mmol) was added to a solution of ethylenediamine-N,N',N'-triacetic acid tri-t-butyl ester (0.80 g, 1.99 mmol) and chloroacetylpyrrolidine (0.59 g, 3.98 mmol) in anhydrous acetonitrile (20 mL). The mixture was heated to reflux for 60 hours under N_2 and then evaporated. The orange residue was dissolved in a mixture of CH_2Cl_2 and K_2CO_3 (saturated).

The aqueous layer was then separated and extracted twice with CH_2Cl_2. The combined organic phases were washed twice with saturated aqueous K_2CO_3, dried ($MgSO_4$) and evaporated. The resulting orange oil was purified twice on silica gel using centrifugal chromatography (using CH_2Cl_2 as the eluent) to afford the desired compound as a yellow oil (0.48 g, 47%). ^1H NMR ($CDCl_3$) δ 1.44 (s, 27H), 1.86 (m, 2H), 1.94 (m, 2H), 2.87 (s, 4H), 3.45 (s, br, 6H), 3.50 (s, 4H), 3.55 (s, 2H). ES-MS m/z *514 $[M+H]^+$.*

N-[2-(N-acetylpyrrolidine)]ethylenediamine-N,N',N'-triacetic acid·xTFA (apedta)

Trifluoroacetic acid (1.0 mL, 0.49 mmol) was added to a solution of the product from above (0.25 g, 12.98 mmol) in anhydrous CH_2Cl_2 (5 mL) and the mixture was stirred overnight at room temperature under nitrogen. The reaction mixture was evaporated and then lyophilized to afford the desired compound as a pale yellow solid (0.21 g, 74.7%). ^1H NMR (D_2O) δ 1.88 (m, 4H), 3.38 (m, 6H), 3.53 (t, 2H, *J*=4.8 Hz), 3.82 (s, 4H), 4.15 (s, 2H), 4.27 (s, 2H). ^{13}C NMR (D_2O) δ 24.03, 25.66, 46.41, 46.94, 50.28, 53.32, 55.32, 56.00, 56.46, 164.36, 169.51, 172.94. ES-MS *m/z* 346$[M+H]^+$, 368$[M+Na]^+$, 384$[M+K]^+$.

Preparation of $[Ru(apedta)(OH_2)]\cdot 1.2H_2O$

[Aqua[*N*-[2-[bis[(carboxy-κ*O*)methyl]amino-κ*N*]ethyl]-*N*-[2-oxo-2-(1-pyrrolidinyl)ethyl]glycinato-κ*N*,κ*O*] ruthenium (III)].

Apedta (0.37 g, 0.65 mmol) was heated in HCl (1 mM, 6 mL) until completely dissolved. The pH of the solution was then adjusted to pH3.0 with KOH (1 N). $K_2[RuCl_5(OH_2)]$ (0.24 g, 0.65 mmol) was added to the solution and the reaction mixture was heated to 100 °C for 2 hours. The solution was evaporated and purified by size exclusion column chromatography on Sephadex G-10 resin (H_2O) and the resulting solid was dried overnight *in vacuo* at 40 °C to afford a brown crystalline solid (0.062 g, 18.1%). ES-MS *m/z* 467$[M-OH_2+Na]^+$. IR (CsI) ν (cm^{-1}) 1646 (C=O). Anal. Calcd. for $C_{14}H_{22}N_3O_8Ru\cdot 1.2\ H_2O\cdot 0.6$ KCl: C, 31.86; H, 4.66; N, 7.96; Cl, 4.03. Found: C, 31.75; H, 4.54; N, 7.68; Cl, 4.05.

EXAMPLE 50.

AMD8894: Ruthenium (III) complex of N-[2-(N-acetyl-(L)-isoleucyl)]ethylenediamine-N,N',N'-triacetic acid (aiedta).

N-chloroacetyl-(L)-isoleucine t-butyl ester

At 0 °C under nitrogen, a solution of chloroacetyl chloride (0.64 mL, 8.01 mmol) in anhydrous THF (10 mL) was added dropwise to a suspension of (L)-isoleucine *t*-butyl ester (1.2 g, 6.41 mmol) and potassium carbonate (1.33 g, 9.62 mmol) in anhydrous THF (10 mL). The reaction mixture was stirred at 0 °C for 30 minutes and then the mixture was evaporated to give a white residue, which was dissolved in a mixture of CH_2Cl_2 and H_2O. The aqueous layer was washed twice with CH_2Cl_2 and then the organic layer was washed twice with H_2O and twice with NH_4Cl (1 N). The combined organic layers were dried ($MgSO_4$) and evaporated to afford a yellow oil. The crude product was purified by column chromatography on silica gel (5% MeOH/CH_2Cl_2) to afford the desired compound as a yellow oil (0.66 g, 40.9%). ^1H NMR ($CDCl_3$) δ 0.94 (m, 6H), 1.24 (m, 1H), 1.48 (m, 10H), 1.93 (m, 1H), 4.07 (s, 2H), 4.48 (dd, 1H, *J*=6.0 Hz, 3.0 Hz), 7.09 (br d, 1H, *J*=6.0 Hz).

A stirred suspension of N-chloroacetyl-(L)-isoleucine *t*-butyl ester (0.66 g, 2.62 mmol), potassium carbonate (0.46 g, 3.30 mmol) and ethylenediamine-N,N',N'-triacetic acid tri-*t*-butyl ester (0.53 g, 1.31 mmol) in anhydrous acetonitrile (15 mL) was heated to reflux for 60 hours under nitrogen and then evaporated. The light brown residue was partitioned between CH_2Cl_2 and saturated aqueous K_2CO_3. The separated aqueous layer was extracted twice with CH_2Cl_2 and then the combined organic phases were washed twice with K_2CO_3 (saturated) then dried ($MgSO_4$) and evaporated to give an orange oil. The crude product was purified by centrifugal chromatography on silica gel (CH_2Cl_2 treated with 1% NH_4OH) to afford the desired compound as a yellow oil (0.51 g, 63.4%). ^1H NMR ($CDCl_3$) δ 0.89 (m, 6H), 1.20 (m, 1H), 1.45 (m, 10H), 1.86 (m, 1H), 2.81 (m, 4H), 3.29 (s, 2H), 3.34 (s, 2H), 3.39 (s, 4H), 4.40 (dd, 1H, *J*=4.8 Hz), 7.88 (d, 1H, *J*=9.0 Hz). ^{13}C NMR ($CDCl_3$) δ 12.15, 15.94, 25.63, 28.45, 28.53, 38.18, 53.00, 53.45, 56.48, 56.95, 57.22, 58.89, 81.35, 81.70, 81.80, 170.78, 170.90, 171.04, 171.55.

N-[2-(N-acetyl-(L)-isoleucyl)]ethylenediamine-N,N',N'-triacetic acid.xTFA (aiedta).

Trifluoroacetic acid (4.0 mL, 51.9 mmol) was added to a solution of the intermediate from above (0.51 g, 0.83 mmol) in anhydrous CH_2Cl_2 (8 mL) and the mixture was stirred overnight at room temperature under nitrogen. The solvent was

evaporated and the residue lyophilized to afford a pale yellow solid (0.45 mg, 86%). ^{1}H NMR (D_2O) δ 0.89 (m, 6H), 1.20 (m, 1H), 1.45 (m, 1H), 1.93 (m, 1H), 3.32 (t, 2H, *J*=6.0 Hz), 3.40 (t, 2H, *J*=6.0 Hz), 3.82 (s, 2H), 3.88 (s, 2H), 3.96 (s, 4H), 4.33 (d, 1H, *J*=6.0 Hz). ^{13}C NMR (D_2O) δ 11.08, 15.39, 25.05, 36.60, 51.76, 52.03, 55.54, 55.84, 56.64, 58.04, 169.77, 171.49, 172.30, 175.52. ES-MS *m/z* 406 $[M+H]^+$, 428 $[M+Na]^+$, 444 $[M+K]^+$.

Preparation of [Ru(aiedtaK)(OH$_2$)]1.6H$_2$O

[Potassium aqua[*N*-[2-[bis[(carboxy-κ*O*)methyl]amino-κ*N*]ethyl]-*N*-[(carboxy-κ*O*)methyl]glycyl-κ*N*-L-isoleucinato ruthenium (III)].

Aiedta (0.35 g, 0.55 mmol) was heated in aqueous HCl (1 mM, 5.5 mL) until completely dissolved and the pH of the solution was then adjusted to pH=3.0 with KOH (1N). $K_2[RuCl_5(OH_2)]$ (0.21 g, 0.55 mmol) was added to the solution and the reaction mixture was heated at 100 °C for 2 hours. The solution was evaporated and the residue was purified by size exclusion column chromatography on Sephadex G-10 resin (H_2O). The resulting solid was dried overnight *in vacuo* at 40 °C to afford the desired complex as a brown crystalline solid (0.030 g, 8.6%). ES-MS *m/z* 527$[M-OH_2-K+Na+H]^+$, 549$[M-OH_2-K+2Na]^+$. IR (CsI) ν(cm^{-1}) 1626 (C=O). Anal. Calcd. for $C_{16}H_{25}N_3O_{10}RuK \cdot 1.6\ H_2O \cdot 0.6$ KCl: C, 30.35; H, 4.49; N, 6.64; Cl, 3.36. Found: C, 30.48; H, 4.64; N, 6.67; Cl, 3.26.

EXAMPLE 51.

AMD8711: Ruthenium (III) complex of N-benzylethylenediamine-N,N',N'-triacetic acid (bedta).

N-Benzylethylenediamine-N,N',N'-triacetic acid tri-t-butyl ester

Following General Procedure E:

Reaction of ethylenediamine-N,N',N'-triacetic acid tri-*t*-butyl ester (0.734 g, 1.8 mmol) with benzylbromide (0.316 g, 1.8 mmol) afforded, after column chromatography on silica gel (7:1 hexanes: EtOAc), the product (0.496 g, 55%) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 1.40 (s, 18H), 1.42 (s, 9H), 2.80-2.88 (m, 4H), 3.24 (s, 2H), 3.44, (s, 4H), 3.80 (s, 2H), 7.21-7.34 (m, 5H).

N-benzylethylenediamine-N,N',N'-triacetic acid·xTFA (bedta)

Following General Procedure B:

Reaction of the intermediate from above (0.496 g, 1.0 mmol) with TFA (12.6 g, 100 mmol) afforded the product (0.454 g, 82%) as a white solid. ^{1}H NMR (MeOD) δ 3.10 (t, 2H, J = 6.0 Hz), 3.39-3.45 (bs, 6H), 4.09 (s, 2H), 4.59 (s, 2H), 7.47-7.50 (m, 3H), 7.57-7.60 (m, 2H). ^{13}C NMR (MeOD) δ 50.59, 53.04, 56.26, 60.90, 130.66, 131.42, 132.01, 132.78, 169.39, 175.74.

Preparation of K[Ru(Hbedta)Cl$_2$]·1.6H$_2$O
[Potassium Hydrogen aqua[N-[2-[[(carboxy-κO)methyl](carboxymethyl)amino-κN]ethyl]-N-(phenylmethyl)glycinato-κN,κO]dichloro ruthenium (III)].

Following General Procedure C:

Reaction of bedta (0.210 g, 0.38 mmol) with $K_2[RuCl_5(H_2O)]$ (0.142 g, 0.38 mmol) afforded the product (0.0460 g, 21%) as a yellow solid. Anal. Calcd. for $C_{15}H_{18}N_2O_6Cl_2RuK·1.6H_2O·0.1KCl$: C, 31.63; H, 3.75; N, 4.92; Cl, 13.07. Found: C, 31.63; H, 3.96; N, 4.77; Cl, 13.03. IR (CsI) ν (cm^{-1}) 1726 (CO_2H); 1641(CO_2-); 391 (Ru-Cl).

EXAMPLE 52.

AMD8702: Ruthenium (III) complex of N-[(3-carboxy)benzyl]ethylenediamine-N,N',N'-triacetic acid (cbedta).

N-[(3-carboxy)benzyl]ethylenediamine-N,N',N'-triacetic acid·xTFA (cbedta)

To a stirred solution of N-[(3-carboxymethyl)benzyl]ethylenediamine-N,N',N'-triacetic acid tri-*t*-butyl ester (0.771 g, 1.4 mmol) in MeOH (19 mL) and H_2O (6 mL) was added lithium hydroxide (0.236 g, 5.6 mmol) and the reaction was stirred for 16 hours at room temperature (in the absence of light) and then the solvent was evaporated *in vacuo*. This intermediate was used directly in the next step without further purification.

The residue was dissolved in TFA (8.3 g, 73 mmol) and stirred for 16 hours then evaporated *in vacuo*. EtOH was added to the residue, the resulting suspension was filtered, and the product lyophilized to afford a white solid (1.04 g, 100%). ^{1}H NMR (MeOD) δ 3.15 (t, 2H, J = 6 Hz), 3.43-3.48 (bs, 6H), 4.09 (s, 2H), 4.64 (s, 2H), 7.59 (dd, 1H, J = 6.0, 9.0 Hz), 7.85 (d, 1H, J = 6.0 Hz), 8.12 (d, 1H, J = 9.0 Hz), 8.26

(s, 1H). ^{13}C NMR (MeOD) δ 50.47, 53.65, 54.16, 60.01, 65.74, 130.65, 132.05, 132.30, 133.13, 133.48, 136.67, 168.93, 169.07, 175.12. ES-MS *m/z* 369 $[M+H]^+$.

Preparation of $K[Ru(H_2cbedta)Cl_2]\cdot 4.5H_2O$

[Potassium Dihydrogen [3-[[[(carboxy-κO)methyl][2-[[(carboxy-κO)methyl](carboxymethyl) amino-κN]ethyl]amino-κN]methyl]benzoato]dichloro ruthenium (III)].

Following General Reaction C:

Reaction of cbedta (0.377 g, 0.60 mmol) with $K_2[RuCl_5(H_2O)]$ (0.236 g, 0.60 mmol) afforded the product (51.0 mg, 12%) as a yellow solid. Anal. Calcd. for $C_{16}H_{18}N_2O_8Cl_2RuK\cdot 4.5H_2O\cdot 0.1KCl$: C, 28.86; H, 4.09; N, 4.21; Cl, 11.18. Found: C, 28.63; H, 3.69; N, 4.29; Cl, 11.08. IR (CsI) ν (cm^{-1}) 1709 (CO_2H); 389 (Ru-Cl).

EXAMPLE 53.

AMD8849: Ruthenium (III) complex N,N'-bis[2-(N-acetylpyrrolidine)] ethylenediamine-N,N'-diacetic acid (bpedda).

N,N'-bis[2-(N-acetylpyrrolidine)]ethylenediamine-N,N'-diacetic acid (bpedda)

A solution of pyrrolidine (0.56 g, 3.90 mmol) in anhydrous THF (20 mL) was added dropwise to a stirred solution of ethylenediamine-N,N,N',N'-tetraacetic acid dianhydride (1.0 g, 7.81 mmol) in anhydrous THF (20 mL) under nitrogen and the mixture was stirred for 15.5 hours. The precipitate which formed was collected by filtration and dried *in vacuo* overnight to give the product as a white solid (1.59 g, ~ 100%). ^1H NMR (D_2O) δ 1.90 (m, 8H), 3.40 (q, 8H, *J*=7.2 Hz), 3.52 (s, 4H), 3.83 (s, 4H), 4.13 (s, 4H). ES-MS *m/z* 399 $[M+H]^+$, 421 $[M+Na]^+$. Anal. Calcd. for $C_{18}H_{30}N_4O_6\cdot 0.2\ H_2O$: C, 53.77; H, 7.62; N, 13.93. Found: C, 53.68; H, 7.54; N, 13.71.

Preparation of $[Ru(bpedda)Cl(OH_2)]\cdot 3H_2O$

[Aquachloro[[*N,N'*-1,2-ethanediylbis[*N*-[2-oxo-2-(1-pyrrolidinyl)ethyl]glycinato-κ*N*,κ*O*]]] ruthenium (III)].

Bpedda (0.50 g, 1.26 mmol) was heated in aqueous HCl (1 mM, 10 mL) until completely dissolved. $K_2[RuCl_5(OH_2)]$ (0.47, 1.26 mmol) was added to the solution and the reaction mixture was heated at 100 °C for 2 hours. The solution was filtered and the filtrate was evaporated. The residue was purified by size exclusion column

chromatography on Sephadex G-10 resin (H_2O) to afford the desired complex as a red solid (0.039 g, 5.2%). ES-MS *m/z* 498 $[M\text{-}Cl\text{-}H_2O]^+$. IR (KBr) ν ($cm^{-1}$)1626 (C=O). Anal. Calcd. for $C_{18}H_{30}N_4O_7ClRu{\cdot}3H_2O$: C, 35.73; H, 6.00; N, 9.26; Cl, 5.86. Found: C, 35.48; H, 5.50; N, 9.19; Cl, 6.01.

EXAMPLE 54.

AMD7461: Ruthenium (III) complex of 2-Hydroxy-1,3-propanediamine-N,N,N',N'-tetraacetic acid (hpdta).

Preparation of $[Ru(H_2hpdta)(OH_2)(O_3SCF_3)]{\cdot}EtOH$

[Dihydrogen aqua[[*N,N'*-(2-hydroxy-1,3-propanediyl)bis[*N*-(carboxymethyl)glycinato-κ*N,O*]]](trifluoromethanesulfonato-κ*O*) ruthenium (III)].

2-Hydroxy-1,3-propanediamine-N,N,N',N',-tetraaceticacid (0.082 g, 0.25 mmol) was dissolved in EtOH (20 mL) and $[Ru(DMF)_6](OTf)_3$ (0.26 g, 0.25 mmol) was added. The reaction was heated to 69 °C for 3 days with stirring, cooled to room temperature and the resulting precipitate was collected by filtration. The solid was washed with EtOH (10 mL) and Et_2O (2 x 10 mL) to afford the desired product (0.0420 mg, 26%). Anal. Calcd. for $C_{12}H_{18}N_2O_{13}RuF_3S{\cdot}1.0EtOH$: C, 26.50; H, 3.81; N, 4.42. Found: C, 26.60; H, 3.89; N, 4.76. IR (CsI) ν (cm^{-1}) 1744 (CO_2H); 1647 (CO_2-).

EXAMPLE 55.

AMD7462: Ruthenium (III) complex of 1,2-Ethylenediamine-N,N'-diaceticacid (edda).

Preparation of $K[Ru(edda)Cl_2]{\cdot}2.5H_2O$

[Potassium dichloro[[*N,N'*-1,2-ethanediylbis[glycinato-κ*N*,κ*O*]] ruthenium (III)].

1,2-Ethylenediamine-N,N'-diaceticacid (0.130 g, 0.74 mmol) was dissolved in EtOH (20 mL) and $RuCl_3{\cdot}H_2O$ (0.155 g, 0.74 mmol) added. The mixture was heated

to 60 °C during which time a precipitate formed. The solid was collected by filtration and washed with Et_2O to afford the desired product (0.0620 g, 22%) as a brown solid. Anal. Calcd. for $C_6H_{10}N_2O_4Cl_2RuK \cdot 2.1H_2O$: C, 17.03; H, 3.38; N, 6.62; Cl, 16.76. Found: C, 17.40; H, 3.76; N, 6.80; Cl, 17.20. IR (CsI) ν (cm^{-1}) 1640 (CO_2); 318 (Ru-Cl).

EXAMPLE 56.

Synthesis of dithiocarbamate ligands

General Procedure F:

Carbon disulfide (1.5-2 equivalents) was dissolved in anhydrous diethyl ether and cooled to 0 °C in an ice bath. The appropriate amine (1 equivalent) and KOH (1-2 equivalents) were dissolved in anhydrous methanol and added dropwise to the carbon disulfide solution. The reaction mixture was stirred for 3 hours at 0 °C. The solvent was removed and the resulting residue was triturated with diethyl ether. The white solid was filtered and washed with diethyl ether and dried *in vacuo*.

The following ligands were prepared using general procedure F:

Pyrrolidinedithiocarbamic acid potassium salt [$KS_2CNC_4H_8$]

Carbon disulfide (2.16 mL, 36 mmol) was reacted with pyrrolidine (2 mL, 24 mmol) and KOH (1.34 g, 24 mmol) to yield 3.8 g (85%) product. ^1H NMR (D_2O) δ 1.94-1.99 (m, 4H), 3.71-3.76 (m, 4H).

L-Prolinedithiocarbamic acid dipotassium salt [$KS_2CNProK$]

Carbon disulfide (1.04 mL, 17.4 mmol) was reacted with L-proline (1.0 g, 8.7 mmol) and KOH (0.97 g, 17.4 mmol) to yield 1.37 g (59%) product. ^1H NMR (D_2O) δ 1.950-2.05 (m, 3H), 2.25-2.35 (m, 1H), 3.78-3.96 (m, 2H), 4.84 (m, 1H). ^{13}C NMR (D_2O) δ 24.78, 31.62, 55.77, 69.58, 180.32, 205.71.

L-Prolinemethyl ester dithiocarbamic acid potassium salt [$KS_2CNProOMe$]

Carbon disulfide (0.53 mL, 8.8 mmol) was reacted with L-proline methyl ester (0.57 g, 4.4 mmol) and KOH (0.49 g, 8.8 mmol) to yield 0.66 g (62%) product. This

product contained some residual starting material and was used without further purification in the preparation of the ruthenium complexes. ^{1}H NMR (D_2O) δ 2.03-2.17 (m, 3H), 2.41-2.44 (m, 1H), 3.78 (m, 1H), 3.91-3.99 (m, 1H), 4.03 (s, 3H), 4.81-4.85 (m, 0.5H), 5.01 (m, 0.5H). ^{13}C NMR (D_2O) δ 24.71, 31.02, 53.30, 60.83, 66.79, 175.43, 208.26.

N-Methyl-L-isoleucinedithiocarbamic acid dipotassium salt [$KS_2CNMeIleK$]

Carbon disulfide (0.83 mL, 13.8 mmol) was reacted with N-methyl-L-isoleucine (1.0 g, 6.89 mmol) and KOH (0.77 g, 13.8 mmol) to yield 0.73 g (37%) product. This product contained some starting material and was used without further purification in the preparation of the ruthenium complexes. ^{1}H NMR (D_2O) δ 0.91 (t, 3H, *J*=7.5 Hz), 1.00 (d, 3H, *J*=6.6 Hz), 1.14-1.23 (m, 1H), 1.30-1.35 (m, 1H), 1.98 (br m, 1H), 3.38 (br s, 3H), 6.01 (d, 1H, *J*=10.2 Hz).

EXAMPLE 57.

AMD8672: Preparation of Chloro(1,4,7-triazacyclononane)bis-(dimethylsufoxide) ruthenium(II) chloride, [Ru(tacn)(DMSO)$_2$Cl]Cl.

[Chloro[octahydro-1*H*-1,4,7-triazonine-κN^1,κN^4,κN^7]bis[(sulfinyl-κ*S*)bis[methane] ruthenium (II) chloride].

Prepared according to literature procedures: A. Geilenkirchen, P. Neubold, R. Schneider, K. Wieghardt, U. Florke, H-J. Haupt, B. Nuber *J. Chem. Soc., Dalton Trans.* **1994**, 457.

EXAMPLE 58.

AMD8641: Preparation of Trichloro(1,4,7-triazacyclononane) Ruthenium(III): [Ru(tacn)Cl$_3$].

[Trichloro[octahydro-1*H*-1,4,7-triazonine-κN^1,κN^4,κN^7] ruthenium (III)].

Prepared according to literature procedures: A. Geilenkirchen, P. Neubold, R. Schneider, K. Wieghardt, U. Florke, H-J. Haupt, B. Nuber *J. Chem. Soc., Dalton Trans.* **1994**, 457.

EXAMPLE 59.

AMD8671: Preparation of Trichloro (1,4,7-trimethyl-1,4,7-triazacyclononane) Ruthenium (III): [Ru(Me$_3$tacn)Cl$_3$].

[Trichloro[hexahydro-1,4,7-trimethyl-1,4,7-triazonine-κN^1,κN^4,κN^7] ruthenium (III)].

Prepared according to literature procedures: P. Neubold, K. Wieghardt, B. Nuber, J. Weiss *Inorg. Chem.* **1989**, *28*, 459.

EXAMPLE 60.

AMD8670: Preparation of [Ru(tacn)(S$_2$CNMe$_2$)$_2$][PF$_6$]

[(Dimethylcarbamodithioato-κ*S*)(dimethylcarbamodithioato-κ*S*,κ*S*') [octahydro-1*H*-1,4,7-triazonine-κN^1,κN^4,κN^7] ruthenium (III) hexafluorophosphate].

General Procedure G

RuLCl$_3$, where L represents either 1,4,7-triazacyclononane (tacn) or 1,4,7-trimethyl-1,4,7-triazacyclononane (Me$_3$tacn), was suspended in deionized water and heated to 40 °C. Two equivalents of the dithiocarbamic acid salt was added and the reaction continued for 1-1.5 hours during which time the reaction mixture turned a dark blue or purple colour. The reaction mixture was removed from heat and filtered while hot. Saturated NH_4PF_6 was added to the filtrate, which produced a dark precipitate. The solid was filtered and washed with deionized water and diethyl ether and dried *in vacuo*.

Using General Procedure G:

Ru(tacn)Cl$_3$ (0.30 g, 0.89 mmol) was reacted with N,N-dimethyldithiocarbamic acid sodium salt ($NaS_2CNMe_2 \cdot 2H_2O$) (Aldrich, 0.32 g, 1.78 mmol) to yield 0.448 g product (80%). Anal. Calcd. for $C_{12}H_{26}N_5S_4RuPF_6$: C, 23.45; H, 4.26; N, 11.39; S, 20.86. Found: C, 23.23; H, 4.34; N, 11.18; S, 20.61. ES-MS *m/z* 471 $[M\text{-}PF_6]^+$.

EXAMPLE 61.

AMD8803: Preparation of [Ru(tacn)(S_2CNEt_2)$_2$][PF_6].
[(Diethylcarbamodithioato-κ*S*)(diethylcarbamodithioato-κ*S*,κ*S*') [octahydro-1*H*-1,4,7-triazonine-κN^1,κN^4,κN^7] ruthenium (III) hexafluorophosphate].

Using General Procedure G:

Ru(tacn)Cl_3 (0.10 g, 0.29 mmol) was reacted with N,N-diethyldithiocarbamic acid sodium salt ($NaS_2CNEt_2 \cdot 3H_2O$) (Aldrich, 0.134 g, 0.6 mmol) to yield 0.163 g product (81%). Anal. Calcd. for $C_{16}H_{35}N_5S_4RuPF_6$: C, 28.61; H, 5.25; N, 10.43; S, 10.09. Found: C, 28.44; H, 5.12; N, 10.31; S, 19.30. ES-MS *m/z* 527 $[M\text{-}PF_6]^+$.

EXAMPLE 62.

AMD8842: Preparation of [Ru(tacn)($S_2CNC_4H_8$)$_2$][PF_6].
[(1,4-butanediylcarbamodithioato-κ*S*)(1,4-butanediylcarbamodithioato-κ*S*,κ*S*') [octahydro-1*H*-1,4,7-triazonine-κN^1,κN^4,κN^7] ruthenium (III) hexafluorophosphate].

Using General Procedure G:

Ru(tacn)Cl_3 (0.10 g, 0.29 mmol) was reacted with pyrrolidinedithiocarbamic acid potassium salt (0.109 g, 0.59 mmol) to yield 0.11 g of crude product. This crude product was purified by column chromatography on silica gel (MeCN/sat. KNO_3/H_2O 7/1/0.5). The solvent was removed from the combined fractions containing the desired product and the residue was triturated with acetonitrile. The excess KNO_3 was removed by filtration and saturated solution of NH_4PF_6 in methanol was added to the filtrate. The resulting precipitate was collected by filtration and washed with deionized water then diethyl ether and dried *in vacuo* to give the title compound (0.069 g, 36%). Anal. Calcd. for $C_{16}H_{31}N_5S_4RuPF_6 \cdot 0.2H_2O \cdot 0.2NH_4PF_6$: C, 27.30; H, 4.61; N, 10.35; S, 18.22. Found: C, 27.06; H, 4.50; N, 10.23; S, 18.24. ES-MS *m/z* 523 $[M\text{-}PF_6]^+$.

EXAMPLE 63.

AMD8731: Preparation of [Ru(tacn)(S_2CNPro)$_2$][PF_6]

[Dihydrogen ((1-carboxy)-1,4-butanediylcarbamodithioato-κ*S*)((1-carboxy)-1,4-butanediylcarbamodithioato-κ*S*,κ*S*') [octahydro-1*H*-1,4,7-triazonine-κN^1,κN^4,κN^7] ruthenium (III) hexafluorophosphate].

Using General Procedure G:

Ru(tacn)Cl_3 (0.30 g, 0.90 mmol) was reacted with with L-prolinedithiocarbamic acid dipotassium salt (0.48 g, 1.8 mmol) to yield 0.273 g (38%) product. Anal. Calcd. for $C_{18}H_{31}N_5O_4S_4RuPF_6 \cdot 1.8H_2O$: C, 27.43; H, 4.42; N, 8.89; S, 16.27. Found: C, 27.36; H, 4.38; N, 9.07; S, 16.33. ES-MS *m/z* 611 [M-PF_6]$^+$. IR (CsI) ν (cm^{-1}) 1723 (CO_2H).

EXAMPLE 64.

AMD8802: Preparation of [Ru(tacn)(S_2CNProOMe)$_2$][PF_6].

((1-carboxymethyl)-1,4-butanediylcarbamodithioato-κ*S*)((1-carboxymethyl)-1,4-butanediylcarbamodithioato-κ*S*,κ*S*') [octahydro-1*H*-1,4,7-triazonine-κN^1,κN^4,κN^7] ruthenium (III) hexafluorophosphate.

Using General Procedure G:

Ru(tacn)Cl_3 (0.136 g, 0.40 mmol) was reacted with L-proline methyl ester dithiocarbamic acid potassium salt (0.20 g, 0.80 mmol) to yield 0.078 g (25%) product. Anal. Calcd. for $C_{20}H_{35}N_5O_4S_4RuPF_6$: C, 30.65; H, 4.50; N, 8.94; S, 16.35. Found: C, 30.54; H, 4.47; N, 8.81; S, 16.52. ES-MS *m/z* 639 [M-PF_6]$^+$. IR (CsI) ν (cm^{-1}) 1742 (CO_2Me).

EXAMPLE 65.

AMD8801: Preparation of [Ru(tacn)(S_2CNMeIle)$_2$][PF_6].

[Dihydrogen (*N*-methyl-*N*-sec-butylcarboxycarbamodithioato-κ*S*)(*N*-methyl-*N*-sec-butylcarboxycarbamodithioato-κ*S*,κ*S*') [octahydro-1*H*-1,4,7-triazonine-κN^1,κN^4,κN^7] ruthenium (III) hexafluorophosphate].

Using General Procedure G:

Ru(tacn)Cl_3 (0.10 g, 0.30 mmol) was reacted with N-methyl-L-isoleucinedithiocarbamic acid dipotassium salt (0.178 g, 0.60 mmol) to yield 0.068 g

(28%) product. Anal. Calcd. for $C_{22}H_{43}N_5O_4S_4RuPF_6$: C, 32.39; H, 5.31; N, 8.58; S, 15.72. Found: C, 32.41; H, 5.46; N, 8.85; S, 15.58. ES-MS *m/z* 671 $[M\text{-}PF_6]^+$. IR (CsI) ν (cm^{-1}) 1726 (CO_2H).

EXAMPLE 66.

AMD8682: Preparation of [Ru(Me$_3$tacn)(S$_2$CNMe$_2$)$_2$][PF$_6$].
[(Dimethylcarbamodithioato-κ*S*)(dimethylcarbamodithioato-κ*S*,κ*S*') [hexahydro-1,4,7-trimethyl-1,4,7-triazonine-κN^1,κN^4,κN^7] ruthenium (III) hexafluorophosphate].

Using General Procedure G:

$Ru(Me_3tacn)Cl_3$ (0.10 g, 0.264 mmol) was reacted with N,N-dimethyldithiocarbamic acid sodium salt (Aldrich, 0.094 g, 0.528 mmol) to yield 0.10 g crude product. This crude product (0.05 g) was purified by column chromatography on silica gel (MeCN/sat. KNO_3/H_2O 7/1/0.5). The solvent was removed from the combined fractions containing the desired product and the residue was triturated with acetonitrile. The KNO_3 was removed by filtration and a saturated solution of NH_4PF_6 in methanol was added to the filtrate. The resulting precipitate was collected, washed with deionized water and diethyl ether and then dried *in vacuo* to give the title compound (0.030 g, 35%). Anal. Calcd. for $C_{15}H_{33}N_5S_4RuPF_6$: C, 27.39; H, 5.06; N, 10.65; S, 19.50; Cl, 0.00. Found: C, 27.51; H, 5.01; N, 10.58, S, 19.28; Cl, 0.00. ES-MS *m/z* 513 $[M\text{-}PF_6]^+$.

EXAMPLE 67.
AMD8800: Preparation of [Ru(tacn)(mida)][PF$_6$].
[(*N*-(carboxy-κ*O*)-methyl)-*N*-methylglycinato-κ*N*,κ*O*][octahydro-1*H*-1,4,7-triazonine-κN^1,κN^4,κN^7] ruthenium (III) hexafluorophosphate].

$Ru(tacn)Cl_3$ (0.10 g, 0.30 mmol) and N-methyliminodiacetic acid (mida) (0.044 g, 0.30 mmol) were refluxed in deionized water (30 mL) for 3 hours. The reaction mixture was filtered hot to remove any unreacted starting material. Saturated aqueous NH_4PF_6 was added to the filtrate and crystallization was induced by the addition of ethanol. The pale yellow precipitate was collected by filtration, washed with diethyl ether and dried *in vacuo* to yield 0.041 g (26%) product. Anal. Calcd. for

$C_{11}H_{22}N_4O_4RuPF_6$: C, 25.39; H, 4.26; N, 10.77. Found: C, 25.37; H, 4.24; N, 10.59. ES-MS *m/z* 376 $[M\text{-}PF_6]^+$. IR (CsI) ν (cm^{-1}) 1642 (CO_2-).

EXAMPLE 68.

AMD8811: Preparation of [Ru(Hnota)Cl].

[Hydrogen chloro[hexahydro-1,4,7-(tricarboxy-κ*O*,κ*O*'-methyl)-1,4,7-triazonine-κN^1,κN^4,κN^7] ruthenium (III)].

1,4,7-Triazacyclononane-1,4,7-triacetic acid (nota) (0.50 g, 1 mmol) was dissolved in deionized water (5 mL) and the pH adjusted to pH 3-4 with KOH (1 M). An aqueous solution of $K_2[RuCl_5(OH_2)]$ (0.40 g, 1 mmol) was added to the solution and the reaction mixture was heated to reflux for 2 hours. The solution was cooled and an insoluble material was removed by filtration. Addition of ethanol to the filtrate resulted in the precipitation of $[Ru(H_2nota)Cl_2]$ (0.1 g) which was removed by filtration. Upon allowing the filtrate to stand, a second precipitate was obtained which was collected and washed with diethyl ether to give the title compound (0.040 g, 8.5%). Anal. Calcd. for $C_{12}H_{19}N_3O_6RuCl{\cdot}H_2O{\cdot}0.2KCl$: C, 30.62; H, 4.50; N, 8.93; Cl, 9.04. Found: C, 30.48; H, 4.64; N, 8.84; Cl, 9.12. ES-MS *m/z* 403 $[M\text{-}Cl]^+$. IR (CsI) ν (cm^{-1}) 1728, (CO_2H); 1678 (CO_2-).

EXAMPLE 69.

AMD7044: Preparation of $[Ru(terpy)(bpy)Cl][PF_6]$.

[Chloro(2,2'-bipyridine-κN^1,κ$N^{1'}$)(2,2':6'.2"-terpyridine-κN^1,κ$N^{2'}$,κ$N^{1''}$) ruthenium (II) hexafluorophosphate].

General Procedure H:

Terpyridylruthenium trichloride ($Ru(terpy)Cl_3$) (E. C. Constable *et al. New J. Chem.* **1992**, *16*, 855) (0.50 g, 1.13 mmol), bidentate ligand, L (one equivalent) and 4-ethylmorpholine (4 drops) were heated to reflux in methanol (100 mL) for 2 hours. The hot solution was filtered through celite and a saturated solution of NH_4PF_6 in methanol was added to the filtrate. The volume was reduced to approximately one third the original volume at which time a precipitate formed. The crude product was

collected by filtration and purified either by re-crystallization from an MeCN/MeOH solution or by column chromatography on silica gel (7/1/0.5: MeCN/sat. KNO_3/H_2O). Using General Procedure H:

Reaction of Ru(terpy)Cl_3 (0.50 g, 1.13 mmol) and 2,2'-dipyridyl (0.18 g, 1.13 mmol) gave the desired product 0.27 g (35%) following purification by column chromatography on silica gel. ^{1}H NMR (CD_3CN) δ 6.94 (m, 1H), 7.26 (m, 3H), 7.66 (m, 3H), 7.86 (m, 2H), 7.94 (m, 1H), 8.06 (t, 1H, *J*=7.8 Hz), 8.26 (m, 2H), 8.36 (d, 2H, *J*=8.1 Hz), 8.47 (d, 2H, *J*=7.8 Hz), 8.59 (d, 1H, *J*=8.2 Hz), 10.20 (d, 1H, *J*=5.8 Hz). ^{13}C NMR (CD_3CN) δ 123.4, 124.23, 124.49, 124.57, 127.09, 127.90, 128.25, 134.73, 136.55, 137.54, 138.05, 153.13, 153.25, 153.49, 157.25, 159.01, 159.70, 159.75. Anal. Calcd. for $C_{25}H_{19}N_5ClRuPF_6 \cdot 0.2NH_4PF_6$: C, 42.68; H, 2.84; N, 10.35; Cl, 5.04. Found: C, 42.83; H, 2.61; N, 10.54; Cl, 4.91.

EXAMPLE 70.

AMD7054: Preparation of [Ru(terpy)(2-pyridinethione)$_2$Cl][PF_6].

[Chlorobis(2(1*H*)-pyridinethione-κS^2)(2,2':6'.2"-terpyridine-κN^1,κN^2',κN^1")ruthenium (II) hexafluorophosphate].

Using General Procedure H:

Reaction of Ru(terpy)Cl_3 (0.50 g, 1.13 mmol) and 2-mercaptopyridine (0.25 g, 2.27 mmol) gave the desired product (0.263g, 32%) after re-crystallization from MeCN/MeOH. ^{1}H NMR (CD_3CN) δ 6.94 (m, 2H), 7.11 (d, 1H, *J*=7.8 Hz), 7.26 (d, 1H, 5.5 Hz), 7.41 (m, 1H), 7.56 (m, 2H), 7.74 (m, 1H), 7.83 (m, 1H), 8.04-8.21 (m, 5H), 8.28-8.37 (m, 2H), 8.44-8.48 (m, 2H), 9.88 (d, 1H, *J*=5.5 Hz). ^{13}C NMR (CD_3CN) δ 122.04, 123.55, 123.79, 124.03, 124.13, 124.36, 124.60, 125.05, 128.12, 128.41, 137.08, 137.79, 138.29, 139.32, 139.40, 151.45, 152.90, 154.77, 155.61, 156.84, 158.80, 159.12, 159.16, 159.90, 163.65. Anal. Calcd. for $C_{25}H_{21}N_5S_2ClRuPF_6$: C, 40.74; H, 2.87; N, 9.50; S, 8.70; Cl, 4.81. Found: C, 40.82; H, 2.80; N, 9.39; S, 8.66; Cl, 4.88.

EXAMPLE 71.

AMD7055: Preparation of $[Ru(terpy)(2\text{-pyrimidinethione})_2Cl][PF_6]$.

[Chlorobis(2(1*H*)-pyrimidinethione-κS^2)(2,2':6'.2"-terpyridine-κN^1,κ$N^{2'}$,κ$N^{1"}$) ruthenium (II) hexafluorophosphate].

Using General Procedure H:

Reaction of $Ru(terpy)Cl_3$ (0.50 g, 1.13 mmol) and 2-mercaptopyrimidine (0.25 g, 2.28 mmol) gave the desired product (0.073g, 8.6%) following purification by column chromatography on silica gel. ^1H NMR (CD_3CN) δ 6.99-7.05 (m, 2H), 7.43 (m, 1H), 7.55-7.60 (M, 2H), 7.81 (m, 1H), 8.10-8.23 (m, 5H), 8.35-8.39 (m, 2H), 8.47-8.50 (m, 2H), 8.87 (dd, 1H, *J*=4.7, 4.7 Hz), 9.95 (dd, 1H, *J*=5.9, 2.3 Hz). Anal. Calcd. for $C_{23}H_{19}N_7S_2ClRuPF_6$: C, 37.38; H, 2.59; N, 13.27; S, 8.68. Found: C, 38.27; H, 2.39; N, 13.75; S, 8.45.

EXAMPLE 72.

AMD7086: Preparation of $[Ru(terpy)(S_2CNMe_2)Cl][PF_6]$.

[Chloro(dimethylcarbamodithioato-κ*S*,κ*S*')(2,2':6'.2"-terpyridine-κN^1,κ$N^{2'}$,κ$N^{1"}$) ruthenium (III) hexafluorophosphate].

$Ru(terpy)Cl_3$ (0.50 g, 1.14 mmol) and N,N-dimethyldithiocarbamic acid sodium salt (Aldrich, 0.204 g, 1.14 mmol) were heated to reflux in methanol (100 mL) for 2 hours. The hot solution was filtered through celite and the volume of the filtrate was reduced to approximately one half the original volume. Addition of a saturated solution of NH_4PF_6 in methanol to the filtrate resulted in the formation of a precipitate, which was collected by filtration and purified by column chromatography on silica gel (MeCN/sat. KNO_3/H_2O: 7/1/0.5) to give the title compound (0.20g, 28%). Anal. Calcd. for $C_{18}H_{17}N_4S_2ClRuPF_6$: C, 34.05; H, 2.70; N, 8.82; S, 10.10. Found: C, 33.76; H, 2.80; N, 9.62; S, 9.95.

EXAMPLE 73.

AMD7036: Preparation of $[Ru(bpy)_2Cl_2]\cdot 2H_2O$

[Dichlorobis(2,2'-bipyridine-κN^1,κ$N^{1'}$) ruthenium (II) dihydrate].

Prepared according to literature procedures: B. Bosnich, F. P. Dwyer *Aust. J. Chem.* **1966**, *19*, 2229.

EXAMPLE 74.

AMD7037: Preparation of $[Ru(phen)_2Cl_2]\cdot 2H_2O$

[Dichlorobis(1,10-phenanthroline-κN^1,κN^{10}) ruthenium (II) dihydrate].

Prepared according to literature procedures: B. Bosnich, F. P. Dwyer *Aust. J. Chem.* **1966**, *19*, 2229.

EXAMPLE 75.

AMD7039: Preparation of $[Ru(bpy)_2(2\text{-mercaptopyridine})][ClO_4]$.

[Bis(2,2'-bipyridine-κN^1,$\kappa N^{1'}$)(2(1*H*)-pyridinethionato-κN^1,κS^2) ruthenium (II)]. Perchlorate.

Prepared according to literature procedures: B. Kumar Santra, M. Menon, C. Kumar Pal, G. Kumar Lahiri *J. Chem. Soc., Dalton Trans.* **1997**, 1387.

EXAMPLE 76.

AMD7045: Preparation of $[Ru(bpy)_2(2\text{-mercaptopyridine})][PF_6]$.

[Bis(2,2'-bipyridine-κN^1,$\kappa N^{1'}$)(2(1*H*)-pyridinethionato-κN^1,κS^2) ruthenium (II) hexafluorophosphate].

$[Ru(bpy)_2Cl_2]\cdot 2H_2O$ (1.0 g, 1.9 mmol) was dissolved in a 1:1 mixture of methanol water (100 mL). 2-Mercaptopyridine was added to the solution and the reaction mixture was heated to reflux for 1.5 hours. The solution was cooled to room temperature and a saturated solution of NH_4PF_6 in methanol was added. Upon standing a dark purple precipitate formed which was removed by filtration and washed with water. This crude product was purified by column chromatography on silica gel (2:1 wCHCl$_3$MeCN) to give the title compound (0.92 g, 72%). ^{1}H NMR (CD_3CN) δ 6.58-6.27 (m, 1H), 6.76 (d, 1H, *J*=8.16Hz), 7.00-7.02 (m, 1H), 7.13-7.17 (m, 1H), 7.19-7.23 (m, 1H), 7.29-7.34 (m, 1H), 7.55-7.60 (m, 1H), 7.67-7.89 (m, 5H), 8.04 (t, 2H, *J*=7.9 Hz), 8.25 (d, 1H, *J*=5.2 Hz), 8.36 (t, 2H, *J*=8.2 Hz), 8.46 (t, 2H,

J=7.3 Hz), 9.84-9.86 (m, 1H). Anal. Calcd. for $C_{25}H_{20}N_5SRuPF_6$: C, 44.91; H, 3.02; N, 10.48; S, 4.80. Found: C, 44.88; H, 3.02; N, 10.58; S, 4.71.

EXAMPLE 77.

AMD8657: Synthesis of $[Ru(acac)_2(MeCN)_2][CF_3SO_3]$. [Bis(acetonitrile)bis(2,4-pentanedionato-κ*O*,κ*O*') ruthenium (III) trifluoromethanesulfonate].

General Procedure I:

This synthesis was adapted from a literature procedure: Oomura, K.; Ooyama, D.; Satoh, Y.; Nagao, N.; Nagao, H.; Howell, M.; Mukaida, M. *Inorg. Chim. Acta* **1998**, *269*, 342. In a schlenk tube, Ru(β-diketonato)$_3$ was dissolved in acetonitrile (~ 1 g/50 mL) and the mixture was stirred for 5 min at 65 °C to yield a orange/red/purple solution; Trifluoromethanesulfonic acid (1.1-4 equivalents) was then added dropwise. Instantly, the solution became brown/green; a reflux condenser was then attached and the mixture was heated to reflux for 0.5-4 h. The final navy blue (Ru(III)) and/or orange/red/brown (Ru(II)) mixture was concentrated and purified by crystalization or column chromatography.

tris-(2,4-pentanedionato) ruthenium(III) [Ru(acac)$_3$] was Prepared according to procedure adapted from the literature: Johnson, A.; Everett, Jr., G. W. *J. Am. Chem. Soc.* **1972**, *94*, 1419.

Preparation of $[Ru(acac)_2(MeCN)_2][CF_3SO_3]$

Using General Procedure I:

$Ru(acac)_3$ (1.07 g, 2.68 mmol) was dissolved in acetonitrile (50 mL). Addition of Trifluoromethanesulfonic acid (300 μL, 3.39 mmol) yielded the title complex after stirring for 1 h at reflux; crystallization from a 40:1 mixture of Et_2O:CH_2Cl_2 at 5 °C overnight yielded a dark blue, crystalline solid (1.42 g, 96 %). Anal. Calcd. for $C_{15}H_{20}N_2O_7SF_3Ru \cdot H_2O$: C, 31.85; H, 3.91; N, 3.98. Found: C, 32.13; H, 3.87; N, 3.96. ES-MS *m/z* 382 $[M\text{-}CF_3SO_3]^+$. IR (KBr) ν (cm^{-1}) 2326, 2296 (C≡N); 1524 (C=O).

EXAMPLE 78.

AMD8660: Synthesis of $Ru(acac)_2(MeCN)_2$.

[Bis(acetonitrile)bis(2,4-pentanedionato-κ*O*,κ*O*') ruthenium (II)].

Preparation of $Ru(acac)_2(MeCN)_2$

$[Ru(acac)_2(MeCN)_2][CF_3SO_3]$ (0.201 g, 0.378 mmol) was dissolved in EtOH (10 mL) to give a blue solution. Addition of $Me_2NCS_2Na{\cdot}2H_2O$ (0.076 g, 0.426 mmol) afforded an orange/brown solution immediately. The mixture was stirred at room temperature for 5 min and then the solvent was removed under reduced pressure. The orange/brown residue was purified by column chromatography on silica gel; 20:1 CH_2Cl_2:MeOH). The major orange band was collected in several fractions and the solvent removed under reduced pressure to yield a yellow/orange solid (0.094 g, 65 %). Anal. Calcd. for $C_{14}H_{20}N_2O_4Ru{\cdot}0.5C_2H_6O$: C, 37.89; H, 5.18; N, 3.19. Found: C, 38.01; H, 4.99; N, 3.26. ES-MS *m/z* 382 $[M+H]^+$. IR (KBr) ν (cm^{-1}) 2333, 2251 (C≡N); 1566 (C=O).

EXAMPLE 79.

AMD8892: Synthesis of $[Ru(3Meacac)_2(MeCN)_2][CF_3SO_3]$.

[Bis(acetonitrile)bis(3-methyl-2,4-pentanedionato-κ*O*,κ*O*') ruthenium (III) trifluoromethanesulfonate].

tris-(3-methyl-2,4-pentanedionato) ruthenium(III) $[Ru(3Meacac)_3]$ was prepared according to literature procedures: Endo, A.; Shimizu, K.; Satô, G. P. *Chem. Lett.* 1985, 581.

Preparation of $[Ru(3Meacac)_2(MeCN)_2][CF_3SO_3]$

Using General Procedure I:

$Ru(3Meacac)_3$ (0.522 g, 1.19 mmol) was dissolved in acetonitrile. Addition of Trifluoromethanesulfonic acid (115 μL, 1.31 mmol) yielded the title complex after 1 h at reflux; crystallization from a 40:1 mixture of Et_2O:CH_2Cl_2 at 5 °C overnight yielded a dark blue, crystalline solid (0.608 g, 92 %). Anal. Calcd. for $C_{17}H_{24}N_2O_7SF_3Ru$: C, 36.56; H, 4.33; N, 5.02; S, 5.74. Found: C, 36.29; H, 4.34; N, 5.04; S, 5.86. ES-MS *m/z* 410 $[M-CF_3SO_3]^+$. IR (KBr) ν (cm^{-1}) 2316, 2296 (C≡N); 1535 (C=O).

EXAMPLE 80.

AMD8901: Synthesis of Ru(3Meacac)$_2$(MeCN)$_2$
[Bis(acetonitrile)bis(3-methyl-2,4-pentanedionato-κ*O*,κ*O*') ruthenium (II)].

Preparation of Ru(3Meacac)$_2$(MeCN)$_2$
[Ru(3Meacac)$_2$(MeCN)$_2$][CF$_3$SO$_3$] (0.105 g, 0.188 mmol) was dissolved in acetonitrile (25 mL) to give a blue solution. Addition of zinc shavings (~ 12 g) followed by rapid stirring for 4 h at room temperature led to the formation of a bright orange solution. The zinc was removed by filtration, the solvent concentrated in vacuo *and then the mixture was purified by column chromatography on silica gel; 20:1 CH$_2$Cl$_2$:MeOH). The major orange band was collected in several fractions and the solvent removed under reduced pressure to yield a bright orange solid (0.025 g, 32 %). Anal. Calcd. for C$_{16}$H$_{24}$N$_2$O$_4$Ru·0.1CH$_2$Cl$_2$: C, 46.27; H, 5.84; N, 6.70. Found: C, 46.00; H, 5.81; N, 6.43. ES-MS m/z 410 [M+H]$^+$. IR (KBr) ν (cm^{-1}) 2336, 2248 (C≡N); 1555 (C=O).*

EXAMPLE 81.

AMD8883 and AMD8884: Synthesis of Ru(3Clacac)$_2$(MeCN)$_2$ and [Ru(3Clacac)$_2$(MeCN)$_2$][CF$_3$SO$_3$].
[Bis(acetonitrile)bis(3-chloro-2,4-pentanedionato-κ*O*,κ*O*') ruthenium (II)] and [Bis(acetonitrile)bis(3-chloro-2,4-pentanedionato-κ*O*,κ*O*') ruthenium (III) trifluoromethanesulfonate].

tris-(3-chloro-2,4-pentanedionato) ruthenium(III) [Ru(3Clacac)$_3$] was prepared according to literature procedure: Endo, A.; Shimizu, K.; Satô, G. P. *Chem. Lett.* **1985**, 581.

Preparation of Ru(3Clacac)$_2$(MeCN)$_2$ and [Ru(3Clacac)$_2$(MeCN)$_2$][CF$_3$SO$_3$]
Using General Procedure I:

Ru(3Clacac)$_3$ (0.375 g, 0.745 mmol) was dissolved in acetonitrile (25 mL). Trifluoromethanesulfonic acid (220 μL, 2.48 mmol) was added and the mixture was heated to reflux for 1 h; purification by column chromatography on silica gel (20:1 CH_2Cl_2:MeOH) resulted in the isolation of two major bands (orange and blue). The fractions containing the orange band were concentrated to ~ 5 mL and hexanes were added to give a bright orange precipitate of Ru(II)(3Clacac)$_2$(MeCN)$_2$ which was isolated via suction filtration (0.085 g, 25 %). Anal. Calcd. for $C_{14}H_{18}N_2O_4Cl_2Ru·0.4CH_2Cl_2$: C, 35.64; H, 3.91; N, 5.76; Cl, 20.72. Found: C, 35.91; H, 4.07; N, 5.61; Cl, 21.00. ES-MS *m/z* 452 $[M+H]^+$. IR (KBr) ν (cm^{-1}) 2335, 2261 (C≡N); 1543 (C=O).

The fractions containing the blue band were concentrated and the dark blue product was crystallized from a 40:1 mixture of Et_2O:CH_2Cl_2 at 5 °C overnight to

give $[Ru(III)(3Clacac)_2(MeCN)_2][CF_3SO_3]$ (0.155 g, 35%). Anal. Calcd. for $C_{15}H_{18}N_2O_7Cl_2SF_3Ru \cdot 0.1C_4H_{10}O$: C, 30.48; H, 3.16; N, 4.62; S, 5.28; Cl, 11.69. Found: C, 30.56; H, 3.28; N, 4.77; S, 5.29; Cl, 11.70. ES-MS *m/z* 451 $[M\text{-}CF_3SO_3]^+$. IR (KBr) ν (cm^{-1}) 2326, 2298 (C≡N); 1532 (C=O).

EXAMPLE 82.

AMD8881: Synthesis of $[Ru(3Bracac)_2(MeCN)_2][CF_3SO_3]$.
[Bis(acetonitrile)bis(3-bromo-2,4-pentanedionato-κ*O*,κ*O*') ruthenium (III) trifluoromethanesulfonate].

tris-(3-bromo-2,4-pentanedionato) ruthenium(III) [$Ru(3Bracac)_3$] was prepared according to literature procedures: Endo, A.; Shimizu, K.; Satô, G. P. *Chem. Lett.* 1985, 581.

Preparation of $[Ru(3Bracac)_2(MeCN)_2][CF_3SO_3]$
Using General Procedure I:

$Ru(3Bracac)_3$ (0.638 g, 1.00 mmol) was dissolved in acetonitrile (25 mL). Addition of Trifluoromethanesulfonic acid (265 μL, 2.99 mmol) yielded the title complex after 1 h at reflux; the mixture was purified by column chromatography on silica gel (20:1 CH_2Cl_2:MeOH) followed by crystallization from a 40:1 mixture of Et_2O:CH_2Cl_2 at 5 °C overnight, to give a dark blue crystalline solid (0.315 g, 46 %). Anal. Calcd. for $C_{15}H_{18}N_2O_7Br_2SF_3Ru \cdot 0.3\ C_4H_{10}O$: C, 27.39; H, 2.98; N, 3.94; S, 4.51. Found: C, 27.62; H, 2.69; N, 4.25; S, 4.70. ES-MS *m/z* 539 $[M\text{-}CF_3SO_3]^+$. IR (KBr) ν (cm^{-1}) 2326, 2299 ($C{\equiv}N_{sym.}$); 1522 (C=O).

EXAMPLE 83.

AMD8900: Synthesis of $Ru(3Bracac)_2(MeCN)_2$.
[Bis(acetonitrile)bis(3-bromo-2,4-pentanedionato-κ*O*,κ*O*') ruthenium (II)].

Preparation of $Ru(3Bracac)_2(MeCN)_2$
$[Ru(3Bracac)_2(MeCN)_2][CF_3SO_3]$ (0.350 g, 0.508 mmol) was dissolved in acetonitrile (50 mL) to give a blue solution. Addition of basic alumina (~ 15 g) followed by rapid stirring for 2 h at room temperature resulted in the formation of an orange/brown solution. The alumina was removed by filtration, the solvent concentrated under reduced pressure and the residue was purified by column chromatography on silica gel (20:1 CH_2Cl_2:MeOH). The major orange band was collected in several fractions and the solvent was removed under reduced pressure.

The orange residue was recrystallized from acetone:hexanes to yield a bright orange solid (0.115 g, 42 %). Anal. Calcd. for $C_{14}H_{18}N_2O_4Br_2Ru \cdot 0.3C_3H_6O$: C, 32.76; H, 3.72; N, 4.93; Br, 28.12. Found: C, 32.74; H, 3.74; N, 4.96; Br, 28.23. ES-MS *m/z* 540 $[M+H]^+$. IR (KBr) ν (cm^{-1}) 2340, 2263 (C≡N); 1530 (C=O).

EXAMPLE 84.

AMD8910 and AMD8896: Synthesis of [Ru(3Iacac)(acac)(MeCN)$_2$][CF_3SO_3] and [Ru(3Iacac)(MeCN)$_4$][CF_3SO_3].

[Bis(acetonitrile)(2,4-pentanedionato-κ*O*,κ*O*')(3-iodo-2,4-pentanedionato-κ*O*,κ*O*') ruthenium-(III) trifluoromethanesulfonate] and [Tetrakis(acetonitrile)(3-iodo-2,4-pentanedionato-κ*O*,κ*O*') ruthenium (II) trifluoromethanesulfonate].

tris-(3-iodo-2,4-pentanedionato) ruthenium(III) [Ru(3Iacac)$_3$] was prepared according to literature procedures: Endo, A.; Shimizu, K.; Satô, G. P. *Chem. Lett.* **1985**, 581.

Preparation of [Ru(3Iacac)$_2$(MeCN)$_2$][CF_3SO_3] and [Ru(3Iacac)(MeCN)$_4$][CF_3SO_3].
Using General Procedure I:

Ru(3Iacac)$_3$ (0.460 g, 0.593 mmol) was dissolved in acetonitrile (25 mL). Trifluoromethanesulfonic acid (60 μL, 0.678 mmol) was added and the reaction was heated to reflux for 1 hour; the reaction mixture was purified by column chromatography on silica gel (15:1 CH_2Cl_2:MeCN) to give [Ru(3Iacac)(acac)(MeCN)$_2$][CF_3SO_3] as a dark blue crystalline solid (0.089 g, 30 %). Anal. Calcd. for $C_{15}H_{19}N_2O_7ISF_3Ru$: C, 27.45; H, 2.92; N, 4.27; S, 4.88; I, 19.33. Found: C, 27.35; H, 3.00; N, 4.21; S, 4.91; I, 19.46. ES-MS *m/z* 508 $[M-CF_3SO_3]^+$. IR (KBr) ν (cm^{-1}) 2326, 2297, 2249 (C≡N), 1523 (C=O).

Repeating the above procedure with 4 equivalents of Trifluoromethanesulfonic acid followed by silica gel column purification and recrystallization of the product from acetone:hexanes gave [Ru(3Iacac)(MeCN)$_4$][CF_3SO_3] as a grey/purple crystalline solid (0.125 g, 33 %). Anal. Calcd. for $C_{14}H_{18}N_4O_5ISF_3Ru \cdot 0.7\ C_3H_6O$: C, 28.44; H, 3.29; N, 8.24; S, 4.71. Found: C, 28.12; H, 3.20; N, 8.02; S, 4.39. ES-MS *m/z* 491 $[M-CF_3SO_3]^+$. IR (KBr) ν (cm^{-1}) 2339, 2284 (C≡N), 1537 (C=O).

EXAMPLE 85.
AMD8691: Synthesis of [Ru(dpac)$_2$(MeCN)$_2$][CF$_3$SO$_3$].
[Bis(acetonitrile)bis(1,3-diphenyl-1,3-propanedionato-κ*O*,κ*O*') ruthenium (III) trifluoromethanesulfonate].

tris-(1,3-diphenyl-1,3-propanedionato) ruthenium(III) [Ru(dpac)$_3$] was prepared according to procedures adapted from the literature: Endo, A.; Shimizu, K.; Satô, G. P.; Mukaida, M. *Chem. Lett.* **1984**, 437.

Preparation of [Ru(dpac)$_2$(MeCN)$_2$][CF$_3$SO$_3$]
Using General Procedure I:

Ru(dpac)$_3$ (8.103 g, 10.5 mmol) was dissolved in acetonitrile (250 mL). Trifluoromethanesulfonic acid (2.5 mL, 28.2 mmol) was added and the reaction mixture was heated to reflux for 20 mins. The mixture was evaporated to dryness and the residue was purified by column chromatography on silica gel (CH_2Cl_2 → 20:1 CH_2Cl_2:MeOH). The fractions containing the dark green band were combined and evaporated to give a dark green crystalline solid (5.75 g, 70 %). Anal. Calcd. for $C_{35}H_{28}N_2O_7SF_3Ru \cdot 0.4H_2O$: C, 53.49; H, 3.69; N, 3.56; S, 4.08. Found: C, 53.45; H, 3.74; N, 3.43; S, 3.97. ES-MS *m/z* 630 $[M\text{-}CF_3SO_3]^+$. IR (KBr) ν (cm^{-1}) 2363, 2337 (C≡N); 1523 (C=O).

EXAMPLE 86.

AMD8692: Synthesis of Ru(dpac)$_2$(MeCN)$_2$
[Bis(acetonitrile)bis(1,3-diphenyl-1,3-propanedionato-κ*O*,κ*O*') ruthenium (II)].

Preparation of Ru(dpac)$_2$(MeCN)$_2$
$[Ru(dpac)_2(MeCN)_2][CF_3SO_3]$ (0.225 g, 0.289 mmol) was dissolved in CH_2Cl_2 (25 mL) to give a green solution. Addition of basic alumina (~ 10 g) resulted in an instant colour change to orange. The mixture was stirred for 30 min at room temperature, the alumina was removed by filtration and the filtrate was evaporated to dryness to yield a bright orange solid (0.045 g, 25 %). Anal. Calcd. for $C_{30}H_{28}N_2O_4Ru \cdot 0.5H_2O$: C, 64.01; H, 4.57; N, 4.39. Found: C, 64.02; H, 4.58; N, 4.19. ES-MS *m/z* 630 $[M+H]^+$. IR (KBr) ν (cm^{-1}) 2339, 2258 (C≡N), 1516 (C=O).

EXAMPLE 87.

AMD8707: Synthesis of $[Ru(hmac)_2(MeCN)_2][CF_3SO_3]$.

[Bis(acetonitrile)bis(2,2,6,6-tetramethyl-3,5-heptanedionato-κ*O*,κ*O*') ruthenium (III) trifluoromethanesulfonate].

tris-(2,2,6,6-tetramethyl-3,5-heptanedionato) ruthenium(III) $[Ru(hmac)_3]$ was prepared according to literature procedures: Endo, A.; Katjitani, M.; Mukaida, M.; Shimizu, K.; Satô, G. P. *Inorg. Chim. Acta* **1988**, *150*, 25.

Preparation of $[Ru(hmac)_2(MeCN)_2][CF_3SO_3]$

Using General Procedure I:

$Ru(hmac)_3$ (0.145 g, 0.207 mmol) was dissolved in acetonitrile (10 mL). Trifluoromethanesulfonic acid (40 μL, 0.452 mmol) was added and the mixture was heated to reflux for 30 mins. The mixture was evaporated to dryness and the residue was purified by column chromatography on silica gel (CH_2Cl_2: hexanes 1:1 followed by 20:1 CH_2Cl_2:MeOH). The fractions containing the blue band were combined and evaporated to give a dark blue crystalline solid (0.104 g, 67 %). Anal. Calcd. for $C_{27}H_{44}N_2O_7SF_3Ru \cdot 1.6CH_4O$: C, 45.79; H, 6.78; N, 3.73. Found: C, 45.86; H, 6.62; N, 3.34. ES-MS *m/z* 550 $[M\text{-}CF_3SO_3]^+$. IR (KBr) ν (cm^{-1}) 2326, 2297 (C≡N); 1529 (C=O).

EXAMPLE 88.

AMD8658: Synthesis of $Ru(hfac)_2(MeCN)_2$

[Bis(acetonitrile)bis(1,1,1,5,5,5-hexafluoro-2,4-pentanedionato-κ*O*,κ*O*') ruthenium (II)].

tris-(1,1,1,5,5,5-hexafluoro-2,4-pentanedionato) ruthenium(III) $[Ru(hfac)_3]$. The ruthenate complex, $K[Ru(hfac)_3]$, was isolated and then oxidized to $Ru(hfac)_3$ according to a literature procedure: Endo, A.; Katjitani, M.; Mukaida, M.; Shimizu, K.; Satô, G. P. *Inorg. Chim. Acta* **1988**, *150*, 25.

Preparation of $Ru(hfac)_2(MeCN)_2$

Using General Procedure I:

$Ru(hfac)_3$ (4.00 g, 5.54 mmol) was dissolved in acetonitrile (200 mL). Trifluoromethanesulfonic acid (865 μL, 6.06 mmol) was added and the mixture was heated to reflux for 1 hour. The solvent was evaporated and the residue was purified by column chromatography on silica gel (CH_2Cl_2) to give a brown/black crystalline solid (2.71 g, 95 %). Anal. Calcd. for $C_{14}H_8N_2O_4F_{12}Ru$: C, 28.15; H, 1.35; N, 4.69. Found: C, 28.35; H, 1.33; N, 4.62. ES-MS *m/z* 598 $[M+H]^+$. IR (KBr) ν (cm^{-1}) 2357, 2285 (C≡N), 1546 (C=O).

EXAMPLE 89.

AMD8693 and AMD8694: Synthesis of sym *and* asym-*Ru(tfac)$_2$(MeCN)$_2$*
[*sym*-Bis(acetonitrile)bis(1,1,1-trifluoro-2,4-pentanedionato-κ*O*,κ*O*') ruthenium (II)] and [*asym*-Bis(acetonitrile)bis(1,1,1-trifluoro-2,4-pentanedionato-κ*O*,κ*O*') ruthenium (II)].

tris-(1,1,1-trifluoro-2,4-pentanedionato) ruthenium(III) [$Ru(tfac)_3$] was prepared according to literature procedures (a mixture of Δ and Λ-isomers isolated): Endo, A.; Katjitani, M.; Mukaida, M.; Shimizu, K.; Satô, G. P. *Inorg. Chim. Acta* 1988, *150*, 25.

Synthesis of *sym* and *asym*-$Ru(tfac)_2(MeCN)_2$

Following General Procedure I:

A mixture of Δ and Λ-$Ru(tfac)_3$ (1.57 g, 2.80 mmol) in acetonitrile (100 mL). Trifluoromethanesulfonic acid (500 μL, 3.50 mmol) was added and the mixture was heated to reflux for 4 hours during which time the solution turned purple/blue. Addition of basic alumina (~ 50 g) afforded an orange solution containing a mixture of the title complexes. The alumina was removed via filtration and the filtrate was purified by column chromatography on silica gel (20:1 CH_2Cl_2:MeOH) to give three bands which eluted in the following order: *sym*-$Ru(tfac)_2(MeCN)_2$, *sym/asym*-$Ru(tfac)_2(MeCN)_2$ mixture and *asym*-$Ru(tfac)_2(MeCN)_2$. Each fraction was evaporated to dryness to give orange solids; the yields of each compound after recrystallization from acetone/ hexanes were: 0.121 g, 0.319 g and 0.244 g, respectively, affording an overall yield of 48%. Both pure isomers have essentially identical analytical data. Anal. Calcd. for $C_{14}H_{14}N_2O_4F_6Ru \cdot 1.3C_3H_6O$: C, 38.11; H,

3.90; N, 4.95. Found: C, 38.29; H, 3.24; N, 4.97. ES-MS *m/z* 490 $[M+H]^+$. IR (KBr) ν (cm^{-1}) 2345 , 2270 (C≡N); 1591 (C=O).

EXAMPLE 90.

AMD8730 and AMD8710: Synthesis of sym *and* asym-*Ru(tftmac)$_2$(MeCN)$_2$.*
[*sym*-Bis(acetonitrile)bis(1,1,1-trifluoro-5,5-dimethyl-2,4-hexanedionato-κ*O*,κ*O*') ruthenium (II)] and
[*asym*-Bis(acetonitrile)bis(1,1,1-trifluoro-5,5-dimethyl-2,4-hexanedionato-κ*O*,κ*O*') ruthenium (II)].

tris-(1,1,1-trifluoro-5,5-dimethyl-2,4-hexanedionato) ruthenium(III) [Ru(tftmac)$_3$] was prepared according to literature procedure (a mixture of Δ and Λ-isomers isolated): Endo, A.; Katjitani, M.; Mukaida, M.; Shimizu, K.; Satô, G. P. *Inorg. Chim. Acta* **1988**, *150*, 25.

Preparation of *sym* and *asym*-Ru(tftmac)$_2$(MeCN)$_2$

Using General Procedure I:

A mixture of Δ and Λ-Ru(tftmac)$_3$ (1.30 g, 1.89 mmol) was dissolved in acetonitrile (100 mL). Trifluoromethanesulfonic acid (425 μL, 2.97 mmol) was added and the reaction mixture was heated to reflux for 3 hours during which time the solution turned purple. Addition of basic alumina (~ 35 g) afforded an orange solution containing a mixture of the title complexes after stirring for 1.5 h at room temperature. The alumina was removed by filtration and the filtrate was purified by column chromatography on silica gel (CH_2Cl_2). Two compounds were isolated which eluted in the order: *sym*-Ru(tftmac)$_2$(MeCN)$_2$ followed by *asym*-Ru(tftmac)$_2$(MeCN)$_2$. The fractions collected were evaporated to yield orange solids, which were recrystallized from acetone/ hexanes to give 0.098 g and 0.461 g, respectively, affording an overall yield of 64%. Both pure isomers have essentially identical analytical data. Anal. Calcd. for $C_{20}H_{26}N_2O_4F_6Ru \cdot 0.5C_3H_6O$: C, 42.86; H, 4.85; N, 4.65. Found: C, 42.93; H, 4.60; N, 4.77. ES-MS *m/z* 574 $[M+H]^+$. IR (KBr) ν (cm^{-1}) 2330, 2268 (C≡N); 1591 (C=O).

EXAMPLE 91.

AMD8757: Synthesis of [Ru(maltol)$_2$(MeCN)$_2$][CF$_3$SO$_3$].
[Bis(acetonitrile)bis[(3-hydroxy-κ*O*)-2-methyl-4-pyronato-κ*O*'] ruthenium (III) trifluoromethanesulfonate].

Preparation of [Ru(maltol)$_2$(MeCN)$_2$][CF$_3$SO$_3$]
Following General Procedure I:

Ru(maltol)$_3$ (0.210 g, 0.441 mmol) was dissolved in acetonitrile (20 mL). Trifluoromethanesulfonic acid (50 µL, 0.565 mmol) was added and the reaction mixture was heated to reflux for 3 hours. The mixture was evaporated and the residue was purified by column chromatography on silica gel (10:1 CH_2Cl_2: MeOH). The fractions containing the dark green band were combined and evaporated and the residue was then recrystallized from acetone/ hexanes to give a dark green crystalline solid (0.085 g, 35 %). Anal. Calcd. for $C_{17}H_{16}N_2O_9SF_3Ru \cdot 0.4C_3H_6O$: C, 36.09; H, 3.06; N, 4.63. Found: C, 36.06; H, 3.09; N, 4.44. ES-MS *m/z* 434 $[M\text{-}CF_3SO_3]^+$. IR (KBr) ν (cm^{-1}) 2322, 2289 (C≡N), 1602, 1548 (C=O).

EXAMPLE 92.
AMD8695 and AMD8696: Synthesis of [Ru(acac)$_2$(MeCN)$_2$(tmpd)][CF$_3$SO$_3$] and [Ru(acac)$_2$(MeCN)$_2$(tmpd)$_2$][CF$_3$SO$_3$].
[Bis(acetonitrile)bis[4-(hydroxy-κ*O*)-3-penten-2-onato](*N*,*N*,*N*',*N*'-tetramethyl-1,3-propanediamine-κ*N*,κ*N*') ruthenium (III) trifluoromethanesulfonate] and [Bis(acetonitrile)bis[4-(hydroxy-κ*O*)-3-penten-2-onato]bis(*N*,*N*,*N*',*N*'-tetramethyl-1,3-propanediamine-κ*N*) ruthenium (III) trifluoromethanesulfonate].

General Procedure J

In a schlenk tube, $[Ru(acac)_2(MeCN)_2][CF_3SO_3]$ was dissolved in CH_2Cl_2 to give a blue solution Dropwise addition of an amine ligand, resulted in an immediate colour change to red/orange. The mixture was stirred at 40 °C for 0.5-3 h before the solvent was removed under reduced pressure and the red/brown residue was purified by column chromatography on silica gel. The amine ligands used included: N,N,N',N'-tetramethyl-1,3-propanediamine (tmpd), diethylenetriamine (dien), 2-(2-aminoethylamino)ethanol (aeae), N-(2-aminoethyl)-1,3-propanediamine (aepd), N-(3-aminopropyl)-1,3-propanediamine (appd), and L1.

Preparation of $[Ru(acac)_2(MeCN)_2(tmpd)][CF_3SO_3]$ and $[Ru(acac)_2(MeCN)_2(tmpd)_2][CF_3SO_3]$

Using General Procedure J:

Addition of tmpd (135 μL, 0.807 mmol) to a CH_2Cl_2 solution of $[Ru(acac)_2(MeCN)_2][CF_3SO_3]$ (0.353 g, 0.665 mmol) afforded a red/orange solution after 1.5 hours. The mixture was purified by column chromatography on silica gel (20:1 CH_2Cl_2:MeOH) to give a red product and an orange product. The fractions from the red and orange bands were evaporated to give dark red (0.039 g, 9 %) and bright orange (0.069 g, 13 %) solids, respectively. The red solid was characterized as $[Ru(acac)_2(MeCN)_2(tmpd)][CF_3SO_3]$. Anal. Calcd. for $C_{22}H_{38}N_4O_7SF_3Ru \cdot 1.3CH_2Cl_2$: C, 36.25; H, 5.30; N, 7.25. Found: C, 36.18; H, 5.29; N, 7.46. ES-MS *m/z* 512 $[M-CF_3SO_3]^+$. IR (KBr) ν (cm^{-1}) 2361, 2340 (C≡N); 1620, 1524 (C=O). The orange solid was characterized as $[Ru(acac)_2(MeCN)_2(tmpd)_2][CF_3SO_3]$. Anal. Calcd. for $C_{29}H_{56}N_6O_7SF_3Ru \cdot 1.8CH_2Cl_2$: C, 39.27; H, 6.38; N, 8.93. Found: C, 39.18; H, 6.39; N, 9.17. ES-MS *m/z* 642 $[M-CF_3SO_3]^+$. IR (KBr) ν (cm^{-1}) 2300 (C≡N); 1624, 1608, 1548, 1521 (C=O).

EXAMPLE 93.

AMD8704 and AMD8705: **Synthesis of *sym* and *asym*-$[Ru(acac)_2(MeCN)_2(dien)][CF_3SO_3]$.**

[Bis(acetonitrile)[*N*,*N*'-bis[2-(amino-κ*N*)ethyl]amine]bis[4-(hydroxy-κ*O*)-3-penten-2-onato] ruthenium (III) trifluoromethanesulfonate] and [Bis(acetonitrile)[*N*-(2-aminoethyl)-1,2-ethanediamine-κ*N*,κ*N*']bis[4-(hydroxy-κ*O*)-3-penten-2-onato] ruthenium (III) trifluoromethanesulfonate].

Preparation of *sym* and *asym*-$[Ru(acac)_2(MeCN)_2(dien)][CF_3SO_3]$

Following General Procedure J:

Addition of dien (70 μL, 0.613 mmol) to a CH_2Cl_2 solution of $[Ru(acac)_2(MeCN)_2][CF_3SO_3]$ (0.325 g, 0.613 mmol) afforded a red/orange solution after 1 hour. The volume was reduced to 5 mL and Et_2O (~ 50 mL) was added to give an orange/brown precipitate which was removed via filtration. The brilliant orange filtrate was concentrated under reduced pressure and the residue was purified by